EFFICACY AND USEFULNESS OF SGLT2 INHIBITORS IN NIDDM PATIENTS ON THE BACKDROP OF METFORMIN AND SULPHONYL UREA

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Chennai -600032

In partial fulfillment for the degree of

MASTER OF PHARMACY

IN

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By

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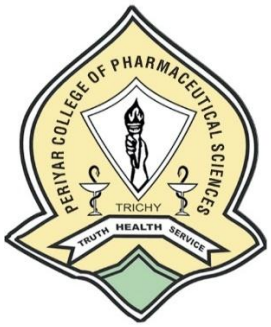

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This is to certify that the dissertation work entitled **"EFFICACY AND USEFULNESS OF SGLT2 INHIBITORS IN NIDDM PATIENTS ON THE BACKDROP OF METFORMIN AND SULPHONYL UREA"** submitted by **M. SRIVIDHYA** for the award of the degree of **"MASTER OF PHARMACY in Pharmacy Practice"** is a bonafide research work done by her in the Department of Pharmacy Practice, Periyar College of Pharmaceutical Sciences, Tiruchirappalli and at the Trichy Diabetes Speciality Centre (P) Ltd., Tiruchirappalli, under my guidance and direct supervision.

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This Dissertation is submitted for acceptance as project for the partial fulfillment of the degree of **"MASTER OF PHARMACY"** in Pharmacy Practice of The Tamilnadu Dr. M. G. R Medical University, Chennai, during October 2016.

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M. Srividhya

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ABBREVIATIONS

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACE	Angiotensin -converting enzyme
ADA	American Diabetes Association
ADVANCE	Action in Diabetes and Vascular disease
ALT	Alanine aminotransferase
AMPK	AMP activated protein kinase
BMI	Body Mass Index
CAD	Coronary Artery Disease
CD3	cluster of differentiation protein
CYP450	cytochrome P 450
DCCT	Diabetes Control and Complication Trial
DM	Diabetes mellitus
DPP-IV	Dipeptidyl peptidase IV
FDA	Food and Drug Administration
FFA	Free fatty acid
GAD	Glutamate decarboxylase
GDM	Gestational Diabetes mellitus
GLP-1	Glucogon –like peptide -1
GLUT 4	Glucose transporter type 4
HbA1c	Haemoglobin A1c
HDLC	High - density lipoprotein cholesterol
HDL	High Density Lipoprotein
HLA	Human leucocyte antigen
ICMR	Indian Council of Medical Research
IDDM	Insulin Dependent Diabetes mellitus
IDF	International Diabetes Federation
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
IRS	Insulin Receptor Substrate
LADA	Latent Autoimmune diabetes in adults
LDLC	Low density lipoprotein cholesterol

LDL	Low Density Lipoprotein
MODY	Maturity onset diabetes of youth
MRDM	Malnutrition related diabetes mellitus
NIDDM	Non-Insulin Dependent Diabetes mellitus
NOD	Non-obese diabetic
NPH	Neutral protamine hagedorn
OGTT	Oral glucose tolerance test
OHA	Oral hypoglycemic drugs
PAI-1	activator -1 plasminogen inhibitor
PPAR-ɣ	Peroxisome proliferator activator receptor -ɣ
SGLT2 –I	Sodium glucose co-transporter type 2 –inhibitor
SU	Sulphonyl urea
TM_G	Transport maximum for glucose
TZD	Thiazolidinedione
UGE	Urinary Glucose Excretion
UKPDS	The United Kingdom Prospective Diabetes Study
VADT	Veteran's Affairs Diabetes Trial

1. INTRODUCTION [1]

Diabetes is a chronic condition that occurs when the body cannot produce enough insulin or cannot use insulin, and is diagnosed by observing raised levels of glucose in the blood. Insulin is a hormone produced in the pancreas; it is required to transport glucose from the bloodstream into the body's cells where it is used as energy. The lack, or ineffectiveness, of insulin in a person with diabetes means that glucose remains circulating in the blood. Over time, the resulting high levels of glucose in the blood (known as hyperglycaemia) causes damage to many tissues in the body, leading to the development of disabling and life-threatening health complications.

Prediabetes

Before people develop type 2 diabetes or non-insulin dependent diabetes mellitus (NIDDM), they almost always have "prediabetes" blood glucose levels that are higher than normal but not yet high enough to be diagnosed as diabetes. Doctors sometimes refer to prediabetes as impaired glucose tolerance (IGT) or impaired fasting glucose (IFG), depending on what test was used when it was detected. This condition puts the patients at a higher risk for developing type 2 diabetes and cardiovascular disease.

Genetics of Type 2 Diabetes

Type 2 diabetes has a stronger link to family history and lineage than type 1, although it too depends on environmental factors. Studies of twins have shown that genetics play a very strong role in the development of type 2 diabetes. Lifestyle also influences the development of type 2 diabetes. Obesity tends to run in families, and families tend to have similar eating and exercise habits. If you have a family history of type 2 diabetes, it may be difficult to figure out whether your diabetes is due to lifestyle factors or genetic susceptibility. Most likely it is due to both.

1.1 HISTORY OF DIABETES MELLITUS [2,3,4]

Diabetes is one of the oldest known diseases. An Egyptian manuscript from c.1550 BCE mentions the phrase "the passing of too much urine."The great Indian physician Sushruta (fl. 6th century BCE) identified the disease and classified it as Medhumeha. He further identified it with obesity and sedentary lifestyle, advising exercises to help "cure" it. The ancient Indians tested for diabetes by observing whether ants were attracted to a person's urine, and called the ailment "sweet urine disease" (Madhumeha).

Concerning the sweetness of urine, it is to be noted that the Chinese, Japanese and Korean words for diabetes are based on the same ideographs which mean "sugar urine disease". It was in 1776 that Matthew Dobson confirmed that the sweet taste comes from an excess of a kind of sugar in the urine and blood.

The first complete clinical description of diabetes was given by the Ancient Greek physician Aretaeus of Cappadocia (fl. 1st century CE), who noted the excessive amount of urine which passed through the kidneys and gave the disease the name "diabetes."

Diabetes mellitus appears to have been a death sentence in the ancient era. Hippocrates makes no mention of it, which may indicate that he felt the disease was incurable. Aretaeus did attempt to treat it but could not give a good prognosis; he commented that "life (with diabetes) is short, disgusting and painful."

In medieval Persia, Avicenna (980-1037) provided a detailed account on diabetes mellitus in The Canon of Medicine, "describing the abnormal appetite and the collapse of sexual functions," and he documented the sweet taste of diabetic urine. Like Aretaeus before him, Avicenna recognized a primary and secondary diabetes. He also described diabetic gangrene, and treated diabetes using a mixture of lupine, trigonella (fenugreek), and zedoary seed, which produces a considerable reduction in the excretion of sugar, a treatment which is still prescribed in modern times. Avicenna also "described diabetes insipidus very precisely for the first time", though it was later Johann Peter Frank (1745-1821) who first differentiated between diabetes mellitus and diabetes insipidus.

Although diabetes has been recognized since antiquity, and treatments of various efficacy have been known in various regions since the Middle Ages, and in legend for much longer, pathogenesis of diabetes has only been understood experimentally since about 1900.The discovery of a role for the pancreas in diabetes is generally ascribed to Joseph von Mering and Oskar Minkowski, who in 1889 found that dogs whose pancreas was removed developed all the signs and symptoms of diabetes and died shortly afterwards. ln 1910, Sir Edward Albert Sharpey-Schafer suggested that people with diabetes were deficient in a single chemical that was normally produced by the pancreas. He proposed calling this substance insulin, from the Latin insula, meaning island, in reference to the insulin-producing islets of Langerhans in the pancreas.

Year 1910

English physiologist Sir Edward Albert Sharpey-Schafer's study of the pancreas leads him to the discovery of a substance that would normally be produced in non-diabetics: insulin. The name comes from the Latin insula, meaning island, referencing the insulin-producing islets of Langerhans in the pancreas.

Year 1916

Elliott Joslin, MD, publishes the first edition of The Treatment of Diabetes Mellitus. A clinician and educator, Joslin is renowned throughout the world as one of the most influential voices in diabetes care.

Year 1921

Frederick Banting, MD, and his then student assistant, Charles Best, MD, extract insulin from dog pancreases. Banting and Best were working in laboratory space at the University of Toronto provided by Professor J.J.R. Macleod. They inject the insulin into dogs whose pancreases have been removed, and the animals' blood sugar levels go down. James Collip purifies the extract so that it can be used in humans. Banting and Macleod were awarded the 1923 Nobel Prize in Physiology or Medicine, though the contributions of all four men have been recognized as important in the discovery of insulin.

Year 1923

Eli Lilly and Company begins commercial production of insulin. In the decades that follow, manufacturers develop a variety of slower-acting insulins, the first being protamine insulin introduced by Novo Nordisk in 1936.

Year 1924

At a time when less than half of all babies born to mothers with diabetes survive, Priscilla White, MD, starts the Joslin Pregnancy Clinic. Fifty years later, Dr. White achieves a 90 percent survival rate among babies born to her patients.

Year 1949

Rachmiel Levine, MD, discovers that insulin works like a key, transporting glucose into cells.

Year 1953

Tablets for testing urine glucose become widely available, and urine test strips appear over the next few years. These options are simpler than using Benedict's solution, which must be mixed with urine and heated over boiling water.

Year 1955

Sulfonylureas, oral medications that stimulate the pancreas to release more insulin, are available. New, more potent forms of these drugs will become available later.

Year 1959

Using radioimmunoassay technology, Solomon Berson, MD and Rosalyn Yalow, PhD develop a method for measuring insulin in the blood. They notice that some people with diabetes still make their own insulin, and they identify "insulin-dependent" (type 1) and "non-insulin-dependent" (type 2) diabetes.

Year 1961

Glucagon, a hormone produced by the pancreas that raises glucose levels, is introduced by Eli Lilly and Company as a treatment for severe hypoglycemia.

Year 1964

The Ames Company introduces the first strips for testing blood glucose by color code.

Year 1966

The first successful pancreas transplant is performed at the University of Minnesota Hospital.

Year 1970

The Ames Company introduces the first glucose meter.

Year 1971

Insulin receptors are discovered on cell membranes. This discovery raises the possibility that missing or defective insulin receptors may prevent glucose from entering the cells, thus contributing to the insulin resistance of type 2 diabetes.

Year 1972

The relationship between blood vessel disease and hyperglycemia is reported.

U100 insulin is introduced. With the availability of this single concentration and with insulin syringes marked with only a U100 scale, frequency of dosing errors could be reduced.

Year 1974

Development of the Biostator enabled continuous glucose monitoring and closed loop insulin infusion. Human Leukocyte Antigens (HLAs) are discovered on cell surfaces. People with type 1 diabetes have specific patterns of HLA that are associated with varying levels of risk for diabetes.

Year 1976

The first insulin pumps were invented.

Year 1977

Rosalyn Yalow, PhD is awarded the Nobel Prize in Physiology and Medicine for her work in measuring insulin in the body.

Boston researchers develop a test to measure glycosylated hemoglobin (A1C). A1c testing becomes the gold standard for measuring long-term diabetes control.

Year 1978

Researchers at the City of Hope National Medical Center in Duarte, California, and Genentech, Inc., in San Francisco, induce E. coli bacteria to produce insulin identical to human insulin. Portable insulin pumps are introduced and researchers achieve normal blood glucose levels in patients using them. But, due to their large size, they are impractical at this time.The National Diabetes Information Clearing house is created by the federal government to gather and document all diabetes literature.

Year 1979

The National Diabetes Data Group develops a new diabetes classification system:

1) insulin-dependent or type 1 diabetes, 2) non-insulin-dependent or type 2 diabetes, 3) gestational diabetes, and 4) diabetes associated with other syndromes or conditions.

Year 1980

A new animal model of type 1 diabetes, the non-obese diabetic (NOD) strain of mouse is described in Japan. Introduction of the basal-bolus concept enabled "intensive insulin therapy" to be used in the clinic to effectively treat people with type 1 diabetes.

Year 1982

The FDA approves human insulin produced by genetically altered bacteria. A 64K autoantibody is discovered and is found to be associated with type 1 diabetes.

Year 1983

A link between hypoglycemia and brain metabolism is established. Second-generation sulfonyl ureas enter the market allowing patients to take smaller doses and with reduced side effects.

Year 1984

The insulin molecule is identified to be a target of autoimmune response in individuals with type 1 diabetes.

Year 1985

Scientists discover a relationship between pregnancy and the worsening of diabetic retinopathy.

Year 1987

The 64K autoantibody originally discovered in 1982 is found to be predictive of type 1 diabetes.

Year 1989

Glucose is discovered to be distributed into muscle and fat cells via a transporter known as GLUT-4. Understanding how glucose is transported from the bloodstream into cells to be used as fuel is important to locating different drug targets that can improve insulin sensitivity.

Year 1990

The 64K autoantibody associated with type 1 diabetes is identified. This protein, GAD, or glutamate decarboxylase, is an important enzyme involved in cellular communication in the brain and pancreas. The immune system's attack on GAD triggers a progressive autoimmune response that leads to diabetes.

Year 1993

The Diabetes Control and Complications Trial (DCCT) showed that keeping blood glucose levels as close to normal as possible slows the onset and progression of eye, kidney, and nerve diseases caused by diabetes. In fact, it demonstrated that any sustained lowering of blood glucose helps, even if the person has a history of poor control.

Year 1994

Captopril is FDA approved to treat end-stage renal disease. Leptin, the fat cell hormone that modulates feeding behavior and hormone secretion, is cloned.

The Scandinavian Simvastatin Survival Study (4S) showed that cholesterol lowering with statins markedly reduced the risk of myocardial infarction, stroke or death. The effect was greatest in individuals with diabetes.

Mid-1990s

The incretin hormone GLP-1 is discovered. Incretin hormones are secreted from the gut in response to food, and encourage the body to produce insulin. Discovery of GLP-1 will later lead to a new class of diabetes drugs that can increase insulin secretion in response to glucose, and even increase the amount of beta cells in the pancreas.

Year 1995

The drug metformin becomes available in the U.S. Metformin is a biguanide that prevents glucose production in the liver.

Year 1996

The drug acarbose, brand name Precose (Bayer Corporation) becomes available in the U.S. Acarbose is an alpha-glucosidase inhibitor that slows digestion of some carbohydrates. Lispro (a lysine-proline analog) is introduced by Eli Lilly and Company as the world's fastest acting insulin.

Year 1997

Troglitazone, brand name Rezulin (Parke-Davis), is approved by the FDA. It is the first in a class of drugs known as thiazolidinediones, and it improves insulin sensitivity in muscle cells. It is eventually removed from the market due to liver toxicity. Rosiglitazone and pioglitazone, also in this drug class, are later brought on to the market.

The terms "insulin-dependent diabetes" (IDDM) and "non-insulin-dependent diabetes" (NIDDM) had long been used to describe different groups of diabetes

patients. The terms type 1 diabetes and type 2 diabetes are now accepted to define diabetes by cause rather than treatment. In addition, the fasting glucose level for diagnosing diabetes is lowered from 140 mg/dl to 126 mg/dl.

Year 1998

Repaglinide, brand name Prandin (Novo Nordisk) is developed. Repaglinide belongs to a class of drugs known as meglitinides. They stimulate insulin secretion in the presence of glucose.

The United Kingdom Prospective Diabetes Study (UKPDS) shows that people with type 2 diabetes who practice tight control of blood sugar levels and blood pressure levels reduce their risk of complications, similar to the results of the DCCT in people with type 1 diabetes. Together these two studies transform the nature of diabetes care around the world.

Year 2002

Treatment with the anti-CD3 monoclonal antibody, hOKT3 gamma1(Ala-Ala), slows the deterioration of insulin production and improves metabolic control during the first year of type 1 diabetes in the majority of patients.

The American Diabetes Association defines prediabetes as impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT). IFG is defined as a fasting blood glucose of 100-125 mg/dl, and IGT is defined as a glucose level from 140 mg/dl – 199 mg/dl two hours after consuming a glucose-rich drink. Later, A1c levels of 5.7% to 6.4% are also used to identify individuals with prediabetes.

Year 2005

Exenatide, brand name Byetta, is approved in the U.S. as a first-in-class incretin mimetic (GLP-1) drug to treat type 2 diabetes. An injectable drug, exenatide works by increasing insulin production in response to blood glucose levels.

Pramlintide, brand name Symlin, is approved in the U.S. as an injectable adjunct treatment for people who use insulin at mealtimes but still fail to achieve desirable glucose levels.

Year 2006

FDA approves JANUVIA (sitagliptin phosphate), the first in a new class of drugs known as DPP-4 inhibitors that enhance the body's ability to lower elevated blood sugar. DPP-4 is an enzyme that naturally blocks GLP-1 from working, so by inhibiting this enzyme, GLP-1 works in the gut to promote insulin secretion.

Year 2008

The results of the ACCORD, ADVANCE and VADT studies are published and presented at the American Diabetes Association Scientific Sessions. All three studies fail to show a benefit of intensive glycemic control on cardiovascular outcomes in people with type 2 diabetes who are at high cardiovascular risk. The results from these studies lead to clinical recommendations that call for a more individualized approach for setting glycemic goals and treatment targets.

Year 2013

FDA approves Invokana (Canagliflozin), the first in a new class of drugs know as the SGLT-2 inhibitors, for lowering elevated blood sugar in patients with type 2 diabetes. SGLT-2 inhibitors block the activity of sodium glucose transport proteins in the kidney, reducing glucose re-uptake and increasing secretion of glucose in the urine.

1.2 EPIDEMIOLOGY [10]

International occurrence

Type 2 diabetes mellitus is less common in non-Western countries where the diet contains fewer calories and daily caloric expenditure is higher. However, as people in these countries adopt Western lifestyles, weight gain and type 2 diabetes mellitus are becoming virtually epidemic.

Rates of diabetes are increasing worldwide. The International Diabetes Federation predicts that the number of people living with diabetes will to rise from 366 million in 2011 to 552 million by 2030. In the United States, the prevalence of diagnosed diabetes has more than doubled in the last 3 decades, largely because of the increase in obesity.

The top 10 countries in number of people with diabetes are currently India, China, the United States, Indonesia, Japan, Pakistan, Russia, Brazil, Italy, and Bangladesh. The greatest percentage increase in rates of diabetes will occur in Africa over the next 20 years. Unfortunately, at least 80% of people in Africa with diabetes are undiagnosed, and many in their 30s to 60s will die from diabetes there.

Race-related demographics

The prevalence of type 2 diabetes mellitus varies widely among various racial and ethnic groups. The image below shows data for various populations. Type 2 diabetes mellitus is more prevalent among Hispanics, Native Americans, African Americans, and Asians/Pacific Islanders than in non-Hispanic whites. Indeed, the disease is becoming virtually pandemic in some groups of Native Americans and Hispanic people. The risk of retinopathy and nephropathy appears to be greater in blacks, Native Americans, and Hispanics.

Age-related demographics

Type 2 diabetes mellitus occurs most commonly in adults aged 40 years or older, and the prevalence of the disease increases with advancing age. Indeed, the aging of the population is one reason that type 2 diabetes mellitus is becoming increasingly common. Virtually all cases of diabetes mellitus in older individuals are type 2.

In addition, however, the incidence of type 2 diabetes is increasing more rapidly in adolescents and young adults than in other age groups. The disease is being recognized increasingly in younger persons, particularly in highly susceptible racial and ethnic groups and the obese. In some areas, more type 2 than type 1 diabetes mellitus is being diagnosed in prepubertal children, teenagers, and young adults. The prevalence of diabetes mellitus by age is shown in the image below.

Prevalence of diabetes in India according to IDF in 2015

- India is home to the second largest number of adults living with diabetes worldwide, after China.
- India is home to the second largest number of children with type 1 diabetes in the world (70,200), after the USA, and accounts for the majority of the children with type 1 diabetes in the region.

India is the largest contributor to regional mortality, with one million deaths attributable to diabetes.

Prevalence in south India

- Prevalence of Diabetes among both urban as well as the rural Indians, with southern India having the **sharpest increase**.
- Indian Council of Medical Research (ICMR) has completed the phase -1 of task force project-ICMR-India Diabetes (INDIAB) Study- Phase- 1 includes the rural and urban settings of Tamilnadu, Jharkhand , Maharashtra, and Chandigarh.
- The adjusted prevalence of Diabetes
    - Tamilnadu 10.4%
    - Jharkhand 5.3%
    - Chandigarh 13.6%
    - Maharashtra

1.3 DIABETES – CLASSIFICATION [5-9]

- Type 1 diabetes: results from the body's failure to produce insulin, and presently requires the person to inject insulin. (Also referred to as insulin-dependent diabetes mellitus, IDDM for short, and juvenile diabetes.)
- Type 2 diabetes: results from insulin resistance, a condition in which cells fail to use insulin properly, sometimes combined with an absolute insulin deficiency. (Formerly referred to as non-insulin-dependent diabetes mellitus, NIDDM for short, and adult-onset diabetes.)
- Gestational diabetes: is when pregnant women, who have never had diabetes before, have a high blood glucose level during pregnancy. It may preceed development of type 2 DM.

Other forms of diabetes mellitus include congenital diabetes, which is due to genetic defects of insulin secretion, cystic fibrosis-related diabetes, steroid diabetes induced by high doses of glucocorticoids, and several forms of monogenic diabetes.

All forms of diabetes have been treatable since insulin became available in 1921, and type 2 diabetes may be controlled with medications. Both type 1 and 2 are chronic conditions that usually cannot be cured. Pancreas transplants have been tried with limited success in type 1 DM; gastric bypass -surgery has been successful in many with morbid obesity and type 2 DM. Gestational diabetes usually resolves after delivery. Diabetes without proper treatments can cause many complications. Acute complications include hypoglycemia, diabetic ketoacidosis, or nonketotic hyperosmolar coma. Serious long-term complications include cardiovascular disease, chronic renal failure, retinal damage. Adequate treatment of diabetes is thus important, as well as blood pressure control and lifestyle factors such as smoking cessation and maintaining a healthy body weight.

1.4 ETIOLOGIC CLASSIFICATION OF DIABETES MELLITUS[6,9,11,12]

I **Type 1** diabetes (β-cell destruction, usually leading to absolute insulin deficiency)

a. Immune mediated

b. Idiopathic

II **Type 2** diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)

III **Other specific types**

a. Genetic defects of n-cell function

i. Chromosome 12, HNF- 1 α (MODY3)

ii. Chromosome 7, glucokinase (MODY2)

iii. Chromosome 20, HNF-4 α (MODY1)

iv. Chromosome 13, insulin promoter factor-1 (IPF-1; MODY4)

v. Chromosome 17, HNF-1 β (MODY5)

vi. Chromosome 2, Neuro D1 (MODY6)

vii. Mitochondrial DNA

viii. Others

b. Genetic defects in insulin action

i. Type A insulin resistance

ii. Leprechaunism

iii. Rabson-Mendenhall syndrome

iv. Lipoatrophic diabetes

v. Others

c. Diseases of the exocrine pancreas

i. Pancreatitis

ii. Trauma/pancreatectomy

iii. Neoplasia

iv. Cystic fibrosis

v. Hemochromatosis

vi. Fibrocalculous pancreatopathy

vii. Others

d. Endocrinopathies

i. Acromegaly

ii. Cushing's syndrome

iii. Glucagonoma

iv. Pheochromocytoma

v. Hyperthyroidism

vi. Somatostatinoma

vii. Aldosteronoma

viii. Others

e. **Drug- / Chemical-induced**

i. Vacor

ii. Pentamidine

iii. Nicotinic acid

iv. Glucocorticoids

v. Thyroid hormone

vi. Diazoxide

vii. β -adrenergic agonists

viii. Thiazides

ix. Dilantin

x. α -Interferon

xi. Others

f. Infections

i. Congenital rubella

ii. Cytomegalovirus

iii. Others

g. Uncommon forms of immune-mediated diabetes

i. “Stiff-man” syndrome

ii. Anti-insulin receptor antibodies

iii. Others

h. Other genetic syndromes sometimes associated with diabetes

i. Down's syndrome

ii. Klinefelter's syndrome

iii. Turner's syndrome

iv. Wolfram's syndrome

v. Friedreich's ataxia

vi. Huntington's chorea

vii. Laurence-Moon-Biedl syndrome

viii. Myotonic dystrophy

ix. Porphyria

x. Prader-Willi syndrome

xi. Others

IV **Gestational diabetes mellitus (GDM)**

i. Type 1 diabetes (β-cell destruction, usually leading to absolute insulin deficiency)

V **Immune-mediated diabetes**

VI **Idiopathic diabetes**

1.5 CAUSES[15]

The cause of diabetes depends on the type. **Type 1 diabetes** is partly inherited and then triggered by certain infection', with some evidence pointing at Coxsackie B4 virus. There is a genetic element it individual susceptibility to some of these triggers which has been traced to particular HLA genotypes (i.e., the genetic "self" identifiers relied upon by the immune system). However, even in those who have inherited the susceptibility type I diabetes mellitus seem to require an environmental trigger. **Type 2 diabetes** is due primarily to lifestyle factors and genetics.

Table 1

Comprehensive list of other causes of diabetes

• Genetic defects of (β-cell Function o Maturity-onset diabetes of young (MODY) o Mitochondrial DNA mutations • Genetic defects in insulin processing or insulin action o Defects in proinsulin conversion o Insulin gene mutations o Insulin receptor mutations • Exocrine Pancreatic Defects o Chronic pancreatitis o Pancreatectomy o Pancreatic neoplasia o Cystic fibrosis o Hemochromatosis o Fibrocalculous pancreatopathy	• Endocrinopathies o Growth hormone excess (acromegaly) o Cushing syndrome o Hyperthyroidism o Pheochromocytoma o Glucagonoma • Infections o Cytomegalovirus infection o Coxsackievirus B • Drugs o Glucocorticoids o Thyroid hormone o β-adrenergic agonists

1.6 COMPARISON OF TYPE 1 AND 2 DIABETES [12]

Table 2

Feature	Type 1 diabetes	Type 2 diabetes
Onset	Sudden	Gradual
Age at onset	Any age (mostly young)	Mostly in adults
Body status	Thin or normal	Often obese
Ketoacidosis	Common	Rare
Autoantibodies	Usually present	Absent
Endogenous insulin	Low or absent	Normal, decreased or increased
Concordance in identical twins	50%	90%
Prevalence	10%	90%

Most cases of diabetes mellitus fall into three broad categories: type 1, type 2, and gestational diabetes. A few other types are described. The term diabetes, usually refers to diabetes mellitus. The rare disease diabetes insipidus has similar symptoms as diabetes mellitus, but without disturbances in the sugar metabolism (insipidus meaning "without taste" in Latin).

The term "type 1 diabetes" has replaced several former terms, including childhood-onset diabetes, juvenile diabetes, and insulin-dependent diabetes mellitus (IDDM). Likewise, the term "type 2 diabetes" has replaced several former terms, including adult-onset diabetes, obesity-related diabetes, and non-insulin dependent diabetes mellitus (NIDDM). Beyond these two types, there is no agreed-upon standard nomenclature. Various sources have defined "type 3 diabetes" as: gestational diabetes, insulin-resistant type 1 diabetes (or "double diabetes"), type 2 diabetes which has progressed to require injected insulin, and latent autoimmune diabetes of adults (or LADA or "type 1.5" diabetes).

Type 1 diabetes

Type 1 diabetes mellitus is characterized by loss of the insulin-producing beta cells of the islets of Langerhans in the pancreas leading to insulin deficiency. This type of diabetes can be further classified as immune-mediated or idiopathic. The majority of type 1 diabetes is of the immune-mediated nature, where beta cell loss is a T-cell mediated autoimmune attack. There is no known preventive measure against type 1 diabetes, which causes approximately 10% of diabetes mellitus cases in North America and Europe. Most affected people are otherwise healthy and of a healthy weight when onset occurs. Sensitivity and responsiveness to insulin are usually normal, especially in the early stages. Type 1 diabetes can affect children or adults but was traditionally termed "juvenile diabetes" because it represents a majority of the diabetes cases in children.

"Brittle" diabetes, also known as unstable diabetes or labile diabetes, is a term that was traditionally used to describe to dramatic and recurrent swings in glucose levels, often occurring for no apparent reason in insulin-dependent diabetes. This term, however, has no biologic basis and should not be used. There are many different reasons for type 1 diabetes to be accompanied by irregular and unpredictable hyperglycemias, frequently with ketosis, and sometimes serious hypoglycemia, including an impaired counter regulatory response to hypoglycemia, occult infection, gastroparesis (which leads to erratic absorption of dietary carbohydrates), and endocrinopathies (eg, Addison's disease). These phenomena are believed to occur no more frequently than in 1% to 2% of persons with type 1 diabetes.

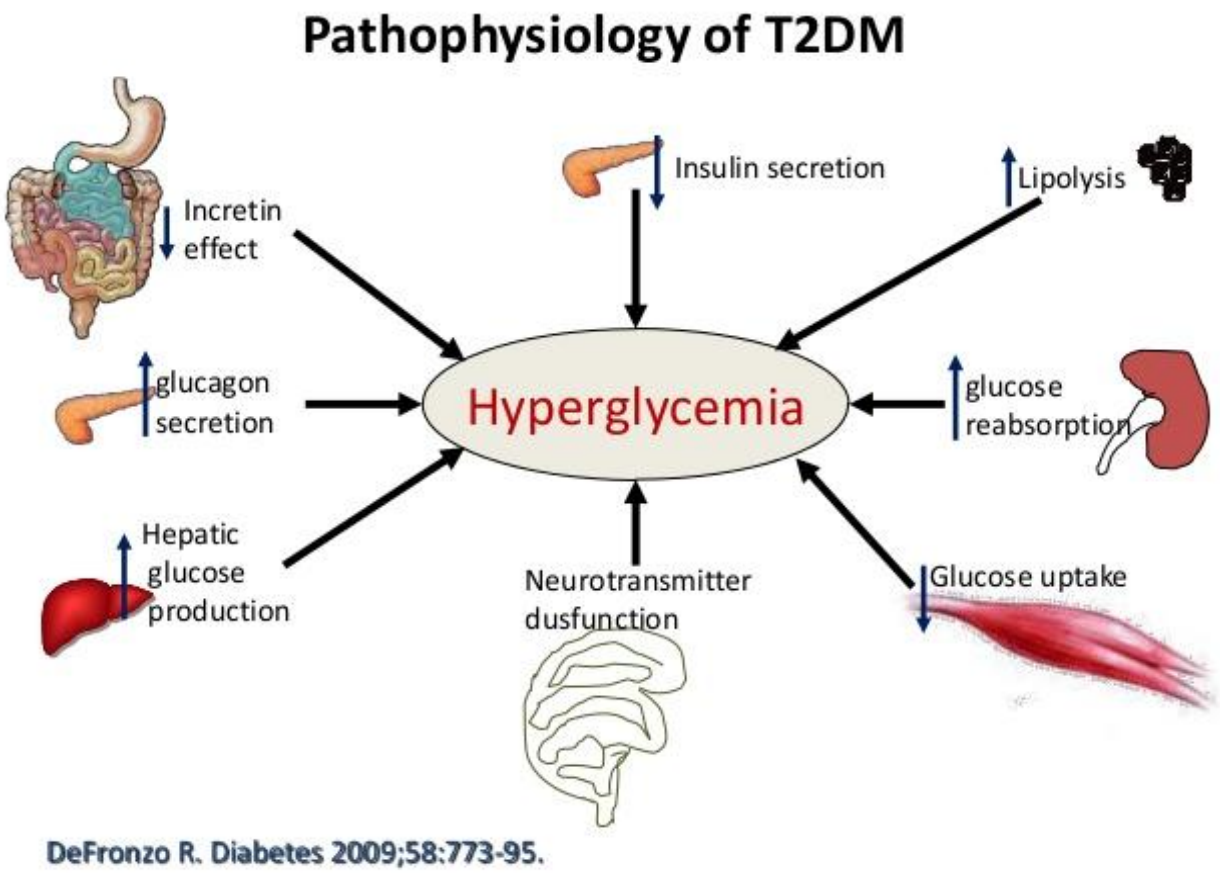
Type 2 diabetes

Type 2 diabetes mellitus is characterized by insulin resistance which may be combined with relatively reduced insulin secretion. The defective responsiveness of body tissues to insulin is believed to involve the insulin receptor. However, the specific defects are not known. Diabetes mellitus due to a known defect are classified separately. Type 2 diabetes is the most common type.

In the early stage of type 2 diabetes, the predominant abnormality is reduced insulin sensitivity. At this stage hyperglycemia can be reversed by a variety of measures and medications that improve insulin sensitivity or reduce glucose production by the liver.

Figure 1

PATHOPHYSIOLOGY OF NIDDM



Gestational diabetes

Gestational diabetes mellitus (GDM) resembles type 2 diabetes in several respects, involving a combination of relatively inadequate insulin secretion and responsiveness. It occurs in about 2%-5% of all pregnancies and may improve or disappear after delivery. Gestational diabetes is fully treatable but requires careful medical supervision throughout the pregnancy. About 20%-50% of affected women develop type 2 diabetes later in life.

Even though it may be transient, untreated gestational diabetes can damage the health of the fetus or mother. Risks to the baby include macrosomia (high birth weight), congenital cardiac and central nervous system anomalies, and skeletal muscle malformations. Increased fetal insulin may inhibit fetal surfactant production and cause respiratory distress syndrome. Hyperbilirubinemia may result from red blood cell destruction. In severe cases, perinatal death may occur, most commonly as a result of poor placental perfusion due to vascular impairment. Labor induction may be indicated with decreased placental function. A cesarean section may be performed if there is marked fetal distress or an increased risk of injury associated with macrosomia, such as shoulder dystocia.

Other types

Pre-diabetes indicates a condition that occurs when a person's blood glucose levels are higher than normal but not high enough for a diagnosis of type 2 diabetes.

Latent autoimmune diabetes of adults is a condition in which Type I diabetes develops in adults. Adults with LADA are frequently initially misdiagnosed as having Type 2 diabetes, based on age rather than etiology.

Some cases of diabetes are caused by the body's tissue receptors not responding to insulin (even when insulin levels are normal, which is what separates it from type 2 diabetes); this form is very uncommon. Genetic mutations (autosomal or mitochondrial) can lead to defects in beta cell function. Abnormal insulin action may also have been genetically determined in some cases. Any disease that causes extensive damage to the pancreas may lead to diabetes (for example, chronic pancreatitis and cystic fibrosis). Diseases associated with excessive secretion of

insulin-antagonistic hormones can cause diabetes (which is typically resolved once the hormone excess is removed). Many drugs impair insulin secretion and some toxins damage pancreatic beta cells. The ICD-10 (1992) diagnostic entity, malnutrition-related diabetes mellitus (MRDM or MMDM, ICD-10 code E12), was deprecated by the World Health Organization when the current taxonomy was introduced in 1999.

Diabetic emergencies

People (usually with type 1 diabetes) may also present with diabetic ketoacidosis, a state of metabolic dysregulation characterized by the smell acetone; a rapid, deep breathing known as Kussmaul breathing; nausea: vomiting and abdominal pain: and altered states of consciousness.

A rare but equally severe possibility is hyperosmolar nonketotic state, which is more common in type 2 diabetes and is mainly the result of dehydration.

1.7 COMPLICATIONS OF DIABETES MELLITUS [13,14]

All forms of diabetes increase the risk of long-term complications. These typically develop after many years (10-20), but may be the first symptom in those who have otherwise not received a diagnosis before that time. The major long-term complications relate to damage to blood vessels. Diabetes doubles the risk of cardiovascular disease. The main "macrovascular" diseases (related to atherosclerosis of larger arteries) are ischemic heart disease (angina and myocardial infarction), stroke and peripheral vascular disease.

Diabetes also causes "microvascular" complications—damage to the small blood vessels. Diabetic retinopathy, which affects blood vessel formation in the retina of the eye, can lead to visual symptoms, reduced vision, and potentially blindness. Diabetic nephropathy, the impact of diabetes on the kidneys, can lead to scarring changes in the kidney tissue, loss of small or progressively larger amounts of protein in the urine, and eventually chronic kidney disease requiring dialysis. Diabetic neuropathy is the impact of diabetes on the nervous system, most commonly causing numbness, tingling and pain in the feet and also increasing the risk of skin damage due to altered sensation. Together with vascular disease in the legs, neuropathy contributes to the risk of diabetes-related foot problems (such as diabetic foot ulcers) that can be difficult to treat and occasionally require amputation.

1. Acute Diabetic ketoacidosis (DKA):

Another acute complication more likely to occur in the IDDM ketoacidosis, is a condition caused by a lack of insulin leading to build-up ketoacids. Ketones are one of the natural by-products of fat metabolism. Excessive ketone bodies are formed by the biochemical imbalance in uncontrolled or poorly managed diabetes. The condition known as diabetic ketoacidosis can directly cause an acute life-threatening event, a diabetic coma. The signs include nausea and vomiting which can lead to loss of water from the body, stomach pain, and deep and rapid breathing. Other signs are a flushed face, dry skin and mouth, a fruity breath odour, a rapid and weak pulse, and low blood pressure. If the person is not given fluids and insulin right away, ketoacidosis can lead to coma and even death.

2.Vascular

a. Microvascular

i. Retinopathy

ii. Neuropathy

iii. Nephropathy

b. Macrovascular

i. Heart disease leading to heart attacks due to high cholesterol level, and smoking (CAD)

ii. Stroke

iii.Peripheral vascular disease which cause other complications like ulcers, gangrene, and amputation

a) Microvascular

i. Retinopathy:

Changes occurring in the eye which are distinctive of diabetes involve the narrowing, hardening, bulging, haemorrhaging or severing of the veins and capillaries of the retina. This is a serious complication known as retinopathy and may lead to loss of vision. Visual changes in the earlier stages may include diminished vision, contraction of the visual field, changes in the size of objects of photophobia. In the more advanced stage, termed 'proliferative retinopathy. haemorrhages, retinal detachment and other serious forms of deterioration are observed. When the disease progresses to this late stage total blindness may occur.

It usually takes between 10-13 years for diabetic retinopathy to develop and it is present in some degree in most diabetics who have had the disease for 21 years. In only about half of the diabetics who develop it however, is vision markedly impaired and blindness occurs in only about 6%. Still, diabetes is the leading cause of blindness in adults 20 to 74 years old and is estimated to cause from

12,000 to 24,000 new cases each year. Two other complications of diabetes. Cataracts and glaucoma, can also lead to loss of vision.

The development of laser therapy will probably reduce the prevalence of diabetes-induced blindness; however this therapy is not without occasional side effects (haemorrhage, retinal detachment and loss of visual field) and is therefore indicated only for the more serious conditions.

ii. Neuropathy:

Diabetic neuropathy results in damage to the nerves.

Neuropathy Classified as:

a. **Peripheral neuropathy**

b. **Autonomic neuropathy**

Diabetic neuropathies are among the most frequent complication of long term diabetes. It is estimated that 60% to 70% of diabetics have mild to severe forms of nervous system damage. The femoral nerve is commonly involved giving rise to symptoms in the legs and feet. Pain is the chief symptom and tends to worsen at night when the person is at rest. It is usually relieved by activity and aggravated by cold. Paraesthesias are a common accompaniment of the pain. Cramping, tenderness and muscle weakness also occur but atrophy is rare. Advanced femoral nerve disease is a major contributing cause of lower extremity amputations. Nerves in the arms, abdomen and back may also be affected. Symptoms may include impaired heart function, slowed digestion, reduced or absent perspiration, severe oedema, carpal tunnel syndrome, alternating bouts of diarrhoea and constipation, bladder atony, urinary and faecal incontinence and impotence.

With respect to sexual impotence, diabetes is probably the single most common disease associated with erectile failure (termed neurogenic impotence in the diabetic). Since diabetes is a metabolic disease with vascular and nervous system complications and an erection involves all levels of the nervous system from the brain to the peripheral nerves, lesions anywhere along the path may be

responsible for erectile failure. It has been estimated that close to 50% of diabetic males have some degree of erectile dysfunction. Neuropathies usually improve with the control of the diabetes. Severe or chronic changes may require several weeks or months to show maximum improvement.

iii. Nephropathy:

Nephropathy is a common and important accompaniment of diabetes and one that in young diabetics takes precedence over heart disease as a cause of illness and death. As with eye changes, there is a wide variation in the type and degree of renal damages. Nephropathy is less frequent than retinopathy and where it occurs is also a development of long standing diabetes. Nevertheless, diabetes is the leading cause of end-stage renal disease in the US, accounting for about 40% of new cases. In 1995, a total of 98,872 people with diabetes underwent dialysis or kidney transplantation and 27,851 developed end-stage renal disease.

One study reported that among 200 juvenile diabetics who survived 20years after onset, one half had evidence of renal disease. Like other long-term complications, good blood glucose control goes a long way towards reducing the risk of diabetic nephropathy. In addition to monitoring the blood sugar levels periodic monitoring of a diabetic patients kidney function (blood urea nitrogen uric acid, creatinine and clearance) is important.

b) **Macro vascular:**

Diabetes is a major risk for morbidity and mortality through atherosclerosis. Coronary and cerebrovascular disease is 2-4 times more common in a diabetic.

Atherosclerosis is a main macrovascular disease. It is extremely common in the community and it's prevalence like diabetes is rapidly increased in our country. The indicating factor for atherosclerosis is deposition of excessive blood cholesterol in the arterial wall.

Ischemic heart disease:

The arteries supplying improper blood to heart, due to this atherosclerosis may result in insufficiency or complete blockage of blood supply. This may lead to chest pain or discomfort or heaviness usually in central pain of chest. Rest relieves angina, sometimes angina starts even at rest and this is a more dangerous variety sometimes patient develop heart attack subsequently, particularly if they do not take care.

Cerebrovascular disease:

Atherosclerosis reduces the blood supply to brain. Due to decrease in blood supply the major blood vessels of brain lead to cerebro vascular disease. Paralytic stroke is one of the common manifestation of cerebrovascular disease. Patient with diabetes are 2-4 times more likely to suffer from stroke than non-diabetic.

Stroke:

Disease caused by damage to blood vessels in the brain. Depending on the part of the brain affected, a stroke can cause a person to lose the ability to speak or move a part of the body such as an arm or a leg. Usually only one side of the body is affected.

1.8 DIAGNOSIS[16,17]

Diabetes diagnostic criteria

Table 3

Condition	2 hour glucose mmol/l(mg/dL)	Fasting glucose mmol/1(mg/dL)	Glycated hemoglobin %
Normal	<7.8 (<140)	<6.1 (<110)	<6.0
Impaired fasting glycaemia	<7.8 (<140)	≥6.1(≥110) & <7.0(<126)	6.0-6.4
Impaired glucose tolerance	≥7.8 (>140)	<7.0 (<126)	6.0-6.4
Diabetes mellitus	≥11.1 (>200)	≥7.0 (>126)	≥6.5

Diabetes mellitus is characterized by recurrent or persistent hyperglycemia, and is diagnosed by demonstrating any one of the following:

- Fasting plasma glucose level ≥ 7.0 mmol/L (126 mg/dL).
- Plasma glucose ≥ 11.1 mmol/L (200 mg/dL) two hours after a 75 gm Oralglucose load as in a glucose tolerance test.
- Symptoms of hyperglycemia and casual plasma glucose ≥ 11.1mmol/L (200 mg/dL).
- Glycated hemoglobin (HbA1c)≥ 6.5%.

A positive result, in the absence of unequivocal hyperglycemia, should be confirmed by a repeat of any of the above-listed methods on a different day. It is preferable to measure a fasting glucose level because of the ease of measurement and the

considerable time commitment of formal glucose tolerance testing, which takes two hours to complete and offers no prognostic advantage over the fasting test. According to the current definition, two fasting glucose measurements above126 mg/dL(7.0 mmol/L) is considered diagnostic for diabetes mellitus.

People with fasting glucose levels from 100 to 125 mg/dL(5.6 to 6.9 mmol/L) are considered to have impaired fasting glucose. Patients with plasma glucose at or above 140 mg/dL (7.8 mmol/L), but not over 200 mg/dl (11.1 mmol/L), two hours after a 75 gm oral glucose load are considered to have impaired glucose tolerance. Of these two pre-diabetic states, the latter in particular is a major risk factor for progression to full-blown diabetes mellitus as well as cardiovascular disease.

Glycated hemoglobin is better than fasting glucose for determining risks of cardiovascular disease and death from any cause.

2. DRUG TREATMENT OF DIABETES MELLITUS [18]

Pharmacologic therapy of type 2 diabetes has changed dramatically in the last 10 years, with new drugs and drug classes becoming available. These drugs allow for the use of combination oral therapy, often with improvement in glycemic control that was previously beyond the reach of medical therapy.

Agents used in diabetic therapy include the following:

a. Biguanides
b. Sulfonylureas
c. Meglitinide derivatives
d. Alpha-glucosidase inhibitors
e. Thiazolidinediones (TZDs)
f. Glucagonlike peptide–1 (GLP-1) agonists
g. Dipeptidyl peptidase IV (DPP-4) Inhibitors
h. Selective sodium-glucose transporter-2 (SGLT-2) inhibitors
i. Insulins
j. Amylinomimetics
k. Bile acid sequestrants
l. Dopamine agonists

Traditionally, diet modification has been the cornerstone of diabetes management. Weight loss is more likely to control glycemia in patients with recent onset of the disease than in patients who are significantly insulinopenic. Medications that induce weight loss, such as orlistat, may be effective in highly selected patients but are not generally indicated in the treatment of the average patient with type 2 diabetes mellitus.

Patients who are symptomatic at initial presentation with diabetes may require transient treatment with insulin to reduce glucose toxicity (which may reduce beta-cell insulin secretion and worsen insulin resistance) or an insulin secretagogue to rapidly relieve symptoms such as polyuria and polydipsia.

2.1 ORAL HYPOGLYCAEMIC DRUGS [18-22]

i. BIGUANIDES:

These agents are considered the first choice for oral type 2 diabetes treatment. They reduce hyperglycemia by decreasing hepatic gluconeogenesis (primary effect) and increasing peripheral insulin sensitivity (secondary effect). They do not increase insulin levels or cause weight gain. Alone, they rarely cause hypoglycemia.

Metformin

Metformin is used as monotherapy or in combination with sulfonylureas, thiazolidinediones, or insulin. It is taken with food to minimize adverse GI effects. Metformin is available in immediate-release and extended-release formulations, as well as in combination with other antidiabetic drugs.

Metformin is contraindicated in patients with impaired renal function, as indicated by a serum creatinine level of greater than 1.5 mg/dL in men or of more than 1.4 mg/dL in women, or an estimated GFR of less than 60 mL/min. It also should not be used within 48 hours of IV iodinated contrast medium.

ii. SULFONYLUREAS:

Sulfonylureas are time-honored insulin secretagogues (ie, oral hypoglycemic agents). They have been used as monotherapy and in combination with other oral hypoglycemic agents or with insulin, although glimepiride is the only sulfonylurea approved by the FDA for combination therapy. Sulfonylureas function by stimulating the release of insulin from pancreatic beta cells and can usually reduce HbA1c by 1-2% and blood glucose concentrations by about 20%.

Glyburide (DiaBeta®, Glynase®)

Glyburide is a second-generation sulfonylurea. It is more potent and exhibits fewer drug interactions than first-generation agents. It also has a longer half-life than most sulfonylureas., Glyburide has been used as an alternative to insulin for the treatment of gestational diabetes, although it is not FDA approved for this indication.

Glipizide (Glucotrol®, Glucotrol XL®, Glipizide XL®)

Glipizide is also a second-generation sulfonylurea. It is more potent and exhibits fewer drug interactions than first-generation agents. It may cause more physiologic insulin release with less risk for hypoglycemia and weight gain than other sulfonylureas.

Glimepiride (Amaryl®)

Stimulates insulin secretion from beta cells; may also decrease rate of hepatic glucose production and increase insulin receptor sensitivity.

iii. MEGLITINIDE DERIVATIVES:

Meglitinides are much more short-acting insulin secretagogues than sulfonylureas. Preprandial dosing potentially achieves more physiologic insulin release and less risk for hypoglycemia. Meglitinide monotherapy has efficacy similar to that of sulfonylureas.

Repaglinide (Prandin®)

Repaglinide is probably most useful in patients at increased risk for hypoglycemia who still need an insulin secretagogue. It works by stimulating insulin release from pancreatic beta cells. Better control of postprandial glycemic excursions also may be achieved with repaglinide. It is FDA approved for monotherapy and for combination therapy with metformin or thiazolidinediones.

Nateglinide (Starlix®)

Nateglinide mimics endogenous insulin patterns, restores early insulin secretion, and controls mealtime glucose surges. It works by stimulating insulin release from pancreatic beta cells. It is indicated as monotherapy for type 2 diabetes or as combination therapy with metformin or a thiazolidinedione. Nateglinide is available in 60-mg and 120-mg tablets.

iv. ALPHA-GLUCOSIDASE INHIBITORS:

Alpha-glucosidase inhibitors prolong the absorption of carbohydrates and thus help to prevent postprandial glucose surges. Their induction of flatulence greatly limits their use. Doses of these agents should be titrated slowly to reduce GI intolerance. Their effect on glycemic control is modest, affecting primarily postprandial glycemic excursions.

Acarbose (Precose®)

Acarbose was the first alpha-glucosidase inhibitor approved by the FDA. It is absorbed to a small degree, so liver function abnormalities can occur rarely. It can be used as monotherapy or in combination with other treatment modalities. The modest effect of acarbose on glycemia and its high degree of GI adverse effects (flatulence) limit its use.

Miglitol (Glyset®)

Miglitol is not absorbed, so liver function abnormalities do not occur. It is FDA approved for use as monotherapy or in combination with sulfonylureas. Its modest effect on glycemia and high degree of GI adverse effects (flatulence) limit its use.

v. THIAZOLIDINEDIONES:

Thiazolidinediones reduce insulin resistance in the periphery (ie, they sensitize muscle and fat to the actions of insulin) and perhaps to a small degree in the liver (ie, insulin sensitizers, antihyperglycemics). They activate peroxisome proliferator–activated receptor (PPAR) gamma, a nuclear transcription factor that is important in fat cell differentiation and fatty acid metabolism. The major action of thiazolidinediones is probably actually fat redistribution. These drugs may have beta-cell preservation properties. Thiazolidinediones have moderate glycemic efficacy, between that of alpha-glucosidase inhibitors and sulfonylureas.

Pioglitazone (Actos®)

Pioglitazone is indicated as an adjunct to diet and exercise to improve glycemic control. It improves target-cell response to insulin without increasing insulin secretion

from the pancreas. It also increases insulin-dependent glucose use in skeletal muscle and adipose tissue. Pioglitazone lowers triglycerides more than rosiglitazone, probably because of its PPAR-alpha effect.

Long duration of pioglitazone use and high cumulative doses have been linked with slightly increased risk for bladder cancer. The FDA currently recommends not prescribing pioglitazone for patients with active bladder cancer and using it with caution in patients with a history of bladder cancer.

Rosiglitazone (Avandia®)

Rosiglitazone is an insulin sensitizer with a major effect on the stimulation of glucose uptake in skeletal muscle and adipose tissue. It lowers plasma insulin levels. It is indicated for type 2 diabetes associated with insulin resistance, as monotherapy and in conjunction with sulfonylureas and/or metformin and insulin. It may preserve beta-cell function and yields positive effects on vasculature and inflammation. It changes LDL and HDL particle size. Because of data suggesting an elevated risk of myocardial infarction in patients treated with rosiglitazone, this agent is currently available only via a restricted access program. Patients currently taking rosiglitazone and benefiting from the drug are permitted to continue using it if they choose to do so. Rosiglitazone is available to new patients only if they are unable to achieve glucose control on other medications and are not willing to take pioglitazone, the only other thiazolidinedione.

iv. GLUCAGON LIKE PEPTIDE-1 AGONISTS:

Glucagonlike peptide–1 (GLP-1) agonists mimic the endogenous incretin GLP-1, stimulating glucose-dependent insulin release (as opposed to oral insulin secretagogues, which may cause non–glucose-dependent insulin release and hypoglycemia), reducing glucagon, and slowing gastric emptying.

Exenatide (Byetta®, Bydureon®)

Exenatide is a GLP-1 agonist that improves glycemic control in patients with type 2 diabetes mellitus. Like endogenous incretins, it enhances glucose-dependent insulin secretion by pancreatic beta cells, suppresses inappropriately elevated glucagon

secretion, and slows gastric emptying. The drug's 39–amino acid sequence partially overlaps that of the human incretin GLP-1.

Exenatide is indicated as adjunctive therapy to improve glycemic control in patients with type 2 diabetes who have not achieved glycemic control with metformin or a sulfonylurea. The solution is administered by subcutaneous injection twice daily.

Liraglutide (Victoza®)

Liraglutide is a once-daily injectable GLP-1 receptor agonist that stimulates G-protein in pancreatic beta cells. It increases intracellular cyclic adenosine monophosphate (cAMP), leading to insulin release in the presence of elevated glucose concentrations. Liraglutide is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The drug has not been studied in combination with insulin.

Albiglutide (Tanzeum®)

Albiglutide is a once-weekly GLP-1 receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. It may be used with other antidiabetic agents, although a dose reduction may be needed for insulin secretagogues (eg, sulfonylureas) or insulin if co-administered. GLP-1 receptor agonists augment glucose-dependent insulin secretion.

Dulaglutide (Trulicity®)

Dulaglutide is a glucagonlike peptide-1 (GLP-1) agonist that acts as an incretin mimetic. It increase insulin secretion in the presence of elevated blood glucose, delays gastric emptying to decrease postprandial glucose, and decreases glucagon secretion. It is administered as a once-weekly SC injection. It is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

v. DIPEPTIDYL PEPTIDASE IV (DPP 4) INHIBITORS:

Incretin hormones are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. They increase insulin release and decrease glucagon levels in the circulation in a glucose-dependent manner. DPP-4 degrades

numerous biologically active peptides, including the endogenous incretins GLP-1 and glucose-dependent insulinotropic peptide (GIP). DPP-4 inhibitors prolong the action of incretin hormones.

Sitagliptin (Januvia®)

Sitagliptin demonstrates selectivity for DPP-4 and does not inhibit DPP-8 or DPP-9 activity in vitro at concentrations approximating those from therapeutic doses. Sitagliptin can be used as a monotherapy or in combination with metformin or a thiazolidinedione. It is given once daily and is weight neutral.

Saxagliptin (Onglyza®)

Saxagliptin inhibits DPP-4 and thereby increases concentrations of GLP-1 and GIP, which stimulate insulin release in response to increased blood glucose levels following meals. This action enhances glycemic control. Saxagliptin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Linagliptin (Tradjenta®)

Linagliptin is a DPP-4 inhibitor that increases and prolongs incretin hormone activity. It is indicated for adults with type 2 diabetes mellitus, along with diet and exercise, to lower blood glucose levels. It may be used as monotherapy or in combination with other common antidiabetic medications, including metformin, sulfonylurea, or pioglitazone; it has not been studied in combination with insulin.

Alogliptin (Nesina®)

Selective dipeptidyl peptidase-4 (DPP-4) inhibitor; slows inactivation of incretin hormones (eg, GLP-1, GIP), thereby reducing fasting and postprandial glucose concentrations in a glucose-dependent manner.

viii. AMYLINOMIMETICS:

These agents mimic endogenous amylin effects by delaying gastric emptying, decreasing postprandial glucagon release, and modulating appetite.

Pramlintide (Symlin®, SymlinPen 120®, SymlinPen 60®)

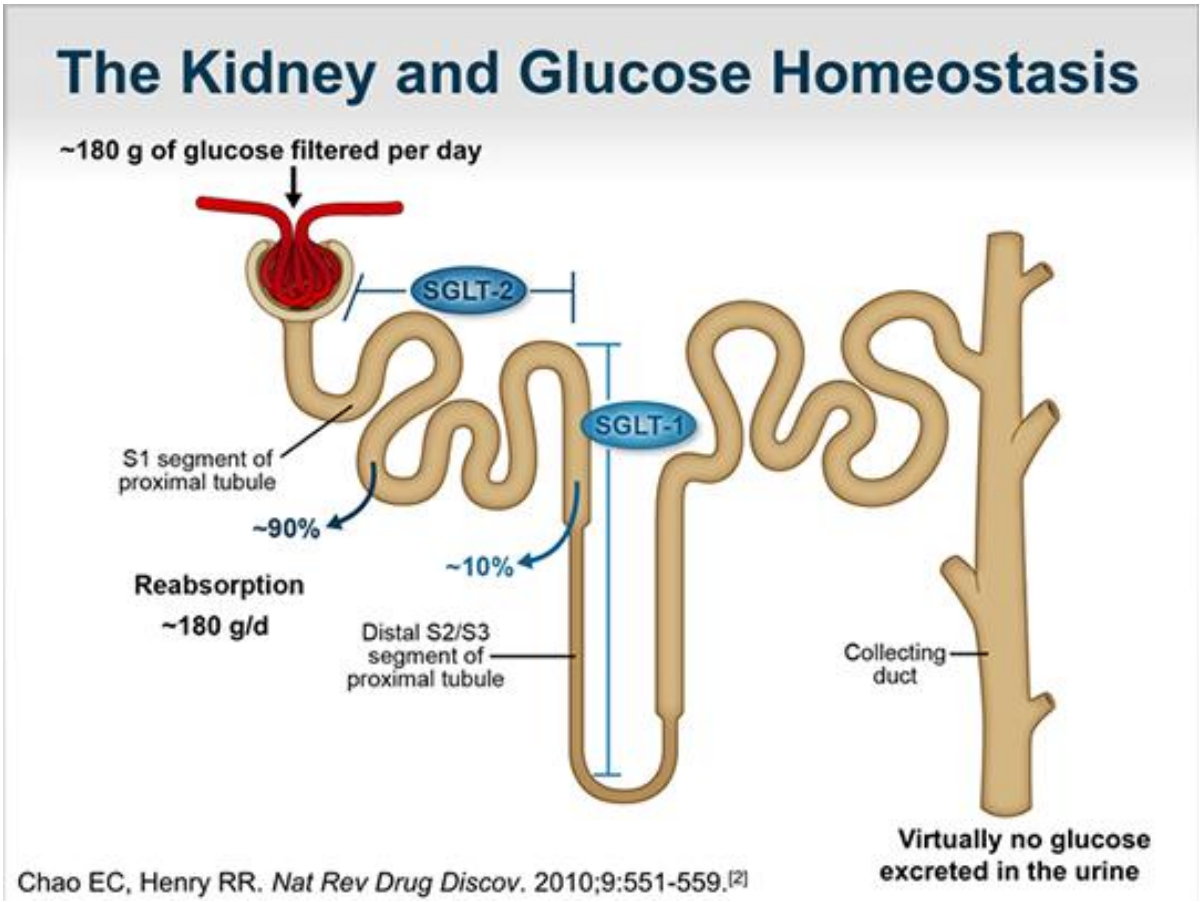
This agent is a synthetic analogue of human amylin, a naturally occurring hormone made in pancreatic beta cells. It slows gastric emptying, suppresses postprandial glucagon secretion, and regulates food intake because of centrally mediated appetite modulation.

Pramlintide is indicated for the treatment of type 1 or type 2 diabetes in combination with insulin. It is administered before mealtime in patients who have not achieved desired glucose control despite optimal insulin therapy.

ix. SODIUM-GLUCOSE TRANSPORTER-2 (SGLT2) INHIBITORS:

Figure 2

Role of SGLT1 and SGLT2 enzymes in the reabsorption of glucose in the kidney



SGLT2 inhibitors lower the renal glucose threshold and around 90% of glucose in the renal filtrate thereby gets excreted.

Canagliflozin (Invokana®)

Canagliflozin, an SGLT-2 inhibitor, lowers the renal glucose threshold (ie, the plasma glucose concentration that exceeds the maximum glucose reabsorption capacity of the kidney). Lowering the renal glucose threshold results in increased urinary glucose excretion.

Dapagliflozin (Farxiga®)

Dapagliflozin reduces glucose reabsorption in the proximal renal tubules and lowers the renal threshold for glucose, thereby increasing urinary glucose excretion. It is indicated as an adjunct to diet and exercise to improve glycemic control in type 2 diabetes mellitus. It is indicated as monotherapy, as initial therapy with metformin, or as an add-on to other oral glucose-lowering agents, including metformin, pioglitazone, glimepiride, sitagliptin, and insulin.

Empagliflozin (Jardiance®)

Empagliflozin, a SGLT2 inhibitor, decreases blood glucose by increasing urinary glucose excretion. SGLT-2 is expressed in the proximal renal tubules and is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. SGLT2 inhibitors reduce glucose reabsorption and lower the renal threshold for glucose.

x. BILE ACID SEQUESTRANTS:

Colesevelam is FDA approved as an adjunctive therapy to improve glycemic control in adults with type 2 diabetes mellitus.

Colesevelam (WelChol®)

Colesevelam is a high-capacity bile acid sequestrant. It is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The precise mechanism by which colesevelam improves glycemic control is largely unknown.

ORAL AGENTS FOR THE TREATMENT OF TYPE 2 DIABETES MELLITUS

Table: 1

SNo	Drug class	Mechanism of action	Daily dosage(mg)	Frequency Per day	Duration of action (hrs)	Main side effects	contraindications	Mode of Excretion
1	**SULFONYLUREA (SU)**							
A	**First generation**							
	Chlorpropamide		100-500	1	24-60	Antabuse like reaction, highest Incidence of hypoglycaemia	Avoid in elderly	Urine
	Tolbutamide		500-2500	2-3	6-12			Urine
	Acetoxamide		250-500	2-3	16			Urine
	Tolazamide		100-500	2-3	24			Urine
B	**Second generation**							
	Glipizide	Increase insulin secretion	2..5-20	1-3	8-12	Hypoglycaemia, Weight gain	Moderate to severe liver dysfunction; adjust dose in severe kidney dysfunction, avoid use of glyburide in elderly patients or patients with kidney dysfunction	Urine 50% Bile 50%
	Glyburide		2.5-20	1-3	8-12			Urine 50% Bile 50%
	Glimepiride		1-8	1	16-24			Urine 60% Bile 40%
	Glipenclamide		2.5-20	1-2	16-24			Urine 50% Bile 50%
	Gliclazide		80-320	1-2	16-24			Urine 50% Bile 20%

S.No	Drug class	Mechanism of action	Daily dosage(mg)	Frequency Per day	Duration of action (hrs)	Main side effects	contraindications	Mode of Excretion
2	**NON –SULFONYLUREA**							
A	**Short acting insulin secretogogues**							
	Repaglinide	Acute increase of insulin secretion	1-6	2-3	2-4	Hypoglycaemia, Weight gain.	Severe liver or kidney dysfunction; Avoid concomitant use of repaglinide with gemfibrosil	Bile
	Nateglinide		120-360	2-3	2-4			Bile
B	**Biguanides**							
	Metformin	Increases liver and muscle insulin sensitivity, decreases Hepatic glucose production	250-2500	2-4	8-12	Gastrointestinal, Lactic acidosis(rare)	Moderate to severe liver or cardiac dysfunction, mild renal dysfunction	Urine 90% Bile 10%
	Metformin ER							Urine 90% Bile 10%
	Phenformin							Urine
C	**Thiazolidinediones**							
	Rosiglitazone	Increases adipose and muscle insulin sensitivity	2-8	1-2	12-24	Weight gain, edema, anemia, Pulmonary edema, congestive heart failure	Malabsorption syndrome, cholestasis	Urine
	Pioglitazone		15-45	1	24			Urine
D	**Alpha glucosidase inhibitors**							
	Acarbose	Delays intestinal carbohydrate absorption	25 mg once daily, titrated to 100 mg 3 times daily	1-3	4	Gastrointestinal	Irritable bowel syndrome, severe kidney or liver dysfunction.	Faeces

2.2 SODIUM GLUCOSE CO-TRANSPORTER TYPE 2 (SGLT2) INHIBITORS[23,29]

Although hyperglycaemia is a key therapeutic focus in the management of patients with type 2 diabetes mellitus (T2DM), many patients experience sub-optimal glycaemic control. Current glucose-lowering agents involve the targeting of various body organ. Sodium glucose co-transporter type 2 (SGLT2) inhibitors target the kidney, reduce renal glucose elimination, thus lowering glucose blood levels.

Glucose reabsorption in the kidney

Overview of renal structure and function

The main structural and functional unit of the kidney is the nephron. A normal human kidney contains approximately 1 million nephrons, with the majority located in the renal cortex and the remainder situated near the cortico-medullary junction. Each nephron consists of a glomerulus, containing afferent and efferent capillaries, and a renal tubule, which includes the glomerular (or Bowman's) capsule, proximal convoluted tubule, loop of Henle, distal convoluted tubule, and the collecting duct. Higher positive pressure in the glomerular blood vessels forces fluid and solutes from the plasma into the glomerular capsule (filtration), and this filtrate then flows through the renal filtrate tubule. Much of this glomerular filtrate undergoes reabsorption into capillary blood via the proximal convoluted tubule. Nitrogenous and other waste products largely remain in the filtrate and pass into the collecting duct, eventually leading to urinary excretion. Other substances (e.g., hydrogen ions, potassium ion, ammonia, and drugs) undergo transport from peritubular capillaries into the renal tubule cells, and then into the filtrate for ultimate urinary excretion via the ureter, bladder, and urethra.

Physiology of renal glucose transport

Key kidney function that help achieve glucose homeostasis involve renal gluconeogenesis, glucose uptake from the circulation, and glucose reabsorption from the glomerular filtrate. Given an average plasma glucose concentration of approximately 100 mg/dL (5.5 mmol/L) and a normal glomerular filtration rate of approximately 180 L/day, healthy individuals filter in the region of 180g/day of

glucose. Virtually all glucose is reabsorbed in the proximal convoluted tubule and returned to the circulation, so that effectively no glucose is excreted in the urine of an otherwise healthy individual. This system is highly efficient and allows conservation of glucose, which is a valuable energy source. 180 g/day of glucose reabsorbed, and the fact that the kidney produce 15-55 g/day of glucose via gluconeogenesis and metabolize 25-35 g/day, renal absorption is a primary mechanism by which the kidney influences glucose homeostasis.

To retrieve glucose in the filtrate, the kidney utilizes two types of membrane-bound carrier proteins: SGLTs (sometimes described as symporters because they transport both glucose and sodium) and the facilitated glucose transporters (GLUTs, sometimes described as uniporters because they only transport glucose).Reabsorption of glucose from the glomerular filtrate is mediated by SGLTs in the proximal convoluted tubule, in a process that is independent of insulin. Approximately 90% of filtrated renal glucose is reabsorbed in the first segment (S1) of the proximal convoluted tubule by SGLT2, a low-affinity high-capacity transporter, and the remaining 10% is removed in the distal segment (S3) by SGLT1, a high-affinity low-capacity transporter. In the kidney, SGLT2 and SGLT1 are located on the luminal surface of epithelial cells lining the proximal convoluted tubule.SGLT2 is expressed to a lower extent in other organs, including the liver, while SGLT1is extensively expressed in the small intestine, where it has significant role in glucose absorption.

SGLTs actively transport glucose against its concentration gradient via coupling to the electrochemical sodium gradient, using energy from a sodium/phosphate adenosine triphosphatase pump. Glucose is released from the proximal convoluted tubule and returned to the blood stream via GLUT2 in the s1/s2 segment and via GLUT1 in the s3 segment of the proximal convoluted tubule. This is a passive process requiring no energy input.

The amount of glucose filtered in the kidney increases linearly with increasing plasma glucose concentration until the transport maximum for glucose(TM_G) beyond the level of the (TM_G), the glucose transport system becomes saturated, therefore any excess glucose remains in the filtrate and is excreted in the urine(ie., glucosuria). In healthy, glucose-tolerant individuals, TM_G is equivalent to a filtration rate of 260-350 mg/min

The plasma glucose concentration at which TM_G is reached is called the renal threshold, and occurs at approximately 200mg/dL (11.0 mmol/L).

Targeting renal glucose reabsorption with SGLT2 inhibitors

Inhibiting SGLT2 provides an attractive addition to the DM treatment armamentarium. SGLT2 inhibitors reduce the TM_G , so less glucose is reabsorbed in the proximal convoluted tubule, they also lower plasma glucose concentration. The net result is increased UGE and decreased hyperglycemia. In addition to potentially improving hyperglycemic symptoms and DM disease complications , normalization of plasma glucose concentration may improve the adverse effects of glucotoxicity, which may contribute to DM itself, by reducing insulin resistance, decreasing hepatic gluconeogenesis, and potentially improving pancreatic beta-cell function.

SGLT2 INHIBITORS

Phlorizin is a naturally occurring glucoside found in various plants, such as the root bark of apple and other fruit trees, and was the prototype SGLT2 inhibitor. First isolated in the 1800s, research into Phlorizin provided the evidence that altered renal glucose excretion could improve glycaemic control. Studied from the 1950s revealed that Phlorizin blocked sugar transport in several tissues, including the kidney and small intestine, and this was subsequently found to be due to inhibition of SGLT protein. Phlorizin was ultimately found to be a competitive inhibitor of SGLT1 and SGLT2, but with a great affinity for SGLT2. In the 1980s, investigators found that Phlorizin-induced UGE was effective in reducing hyperglycaemia via an insulin-independent mechanism, without causing hyperglycaemia. Animal studies also supported the use of Phlorizin in improving insulin sensitivity without affecting insulin action in healthy control animals, with hyperglycaemia and insulin resistance both returning after Phlorizin was unsuitable for clinical development as a therapeutic agent for a number of reasons.

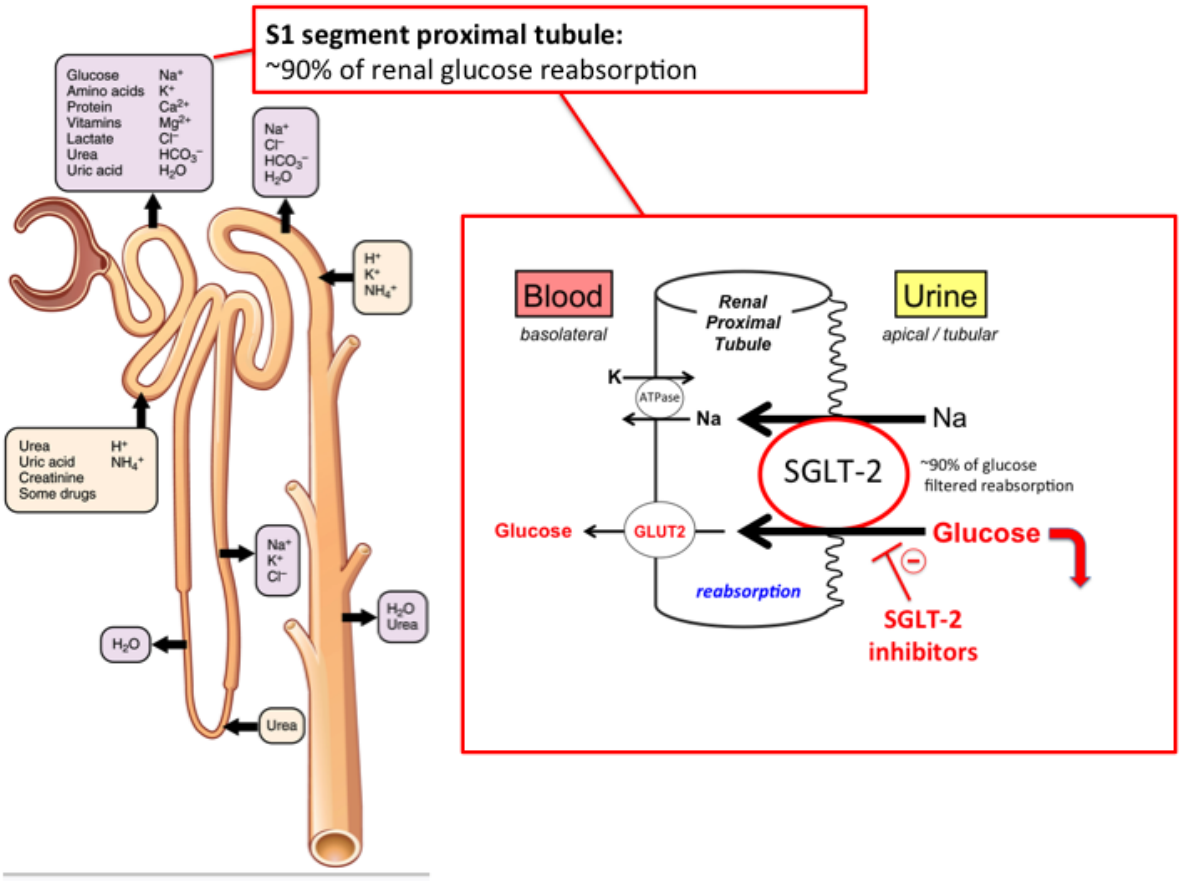
Firstly, Phlorizin has a low selectivity for SGLT2 versus SGLT1, resulting in the inhibition of SGLT1 as well as SGLT2. AsSGLT1 is primarily expressed in the small intestine, where it is responsible for the absorption of glucose and galactose from the

diet, SGLT1 inhibition can result in gastrointestinal side effect such as severe diarrhoea, dehydration, and malabsorption.

Secondly Phlorizin has a low oral bioavailability and is metabolized to Phloretin by glucosidase enzymes in the gut, which means it must be given, which may lead to interference with glucose uptake in various tissues (Eg., the central nervous system) .The first reported SGLT2 inhibitor was T-1095, an orally administered O-glycoside pro-drug that was metabolised in the liver into its active form T-1095A. Its non-selective SGLT1 inhibition led to discontinuation. Then attention turned to the C-glycoside compounds which had the increased metabolic stability.

Figure 3

Mechanism of Action of SGLT2 Inhibitors



Drugs in the SGLT2 inhibitors class include empagliflozin, canagliflozin, dapagliflozin, ipragliflozin (which has not yet been approved for use in the U.S.). At this time canagliflozin is the only drug in this class approved by the FDA for the treatment of type 2 diabetes.

Vaginal yeast infections and urinary tract infections are the most common side effects associated with canagliflozin with the greatest risk being in female patients and those men who are uncircumcised.

There is also an increased desire to urinate and the medication is not indicated in patients with type 1 diabetes, or patients with frequent ketones in their blood or urine, severe renal impairment, end stage renal disease or patients receiving dialysis. Patients should be advised to expect glucose to be in the urine and if they are using urine glucose strips that they will have a positive reading most of the time.

2.3 INSULINS [30,31]

Human Insulin and Insulin Analogs are available for insulin replacement therapy. Insulins also are classified by the timing of their action in your body – specifically, how quickly they start to act, when they have a maximal effect and how long they act. Insulin analogs have been developed because human insulins have limitations when injected under the skin. In high concentrations, such as in a vial or cartridge, human (and also animal insulin) clumps together. This clumping causes slow and unpredictable absorption from the subcutaneous tissue and a dose-dependent duration of action (i.e. the larger dose, the longer the effect or duration). In contrast, insulin analogs have a more predictable duration of action. The rapid acting insulin analogs work more quickly, and the long acting insulin analogs last longer and have a more even, "peakless" effect.

Insulin has been available since 1925. It was initially extracted from beef and pork pancreases. In the early 1980's, technology became available to produce human insulin synthetically.

Characteristics of Insulin

Insulins are categorized by differences in:

- Onset (how quickly they act)
- Peak (how long it takes to achieve maximum impact)
- Duration (how long they last before they wear off)
- Concentration (Insulins sold in the U.S. have a concentration of 100 units per ml or U100. In other countries, additional concentrations are available. Note: If you purchase insulin abroad, be sure it is U100.)
- Route of delivery (whether they are injected under the skin or given intravenously)
- Insulin is usually injected into the fatty tissue just under the skin. This is also called subcutaneous tissue.

Types of Insulin : There are three main groups of insulins:

- Fast-acting
- Intermediate-acting
- Long-acting insulin.

Fast-acting insulin:

- Is absorbed quickly from your fat tissue (subcutaneous) into the bloodstream.
- Is used to control the blood sugar during meals and snacks and to correct high blood sugars

Includes:

Rapid Acting Insulin Analogs (Insulin Aspart, insulin Lyspro, Insulin Glulisine) which have an onset of action of 5 to 15 minutes, peak effect in 1 to 2 hours and duration of action that lasts 4-6 hours. With all doses, large and small, the onset of action and the time to peak effect is similar, The duration of insulin action is, however, affected by the dose – so a few units may last 4 hours or less, while 25 or 30 units may last 5 to 6 hours. As a general rule, assume that these insulins have duration of action of 4 hours.

Regular Human Insulin

Includes

Humulin or Novolin which has an onset of action of 1/2 hour to 1 hour, peak effect in 2 to 4 hours, and duration of action of 6 to 8 hours. The larger the dose of regular the faster the onset of action, but the longer the time to peak effect and the longer the duration of the effect.

Intermediate-acting insulin:

- Is absorbed more slowly, and lasts longer
- Is used to control the blood sugar overnight, while fasting and between meals

Includes:

NPH Human Insulin which has an onset of insulin effect of 1 to 2 hours, a peak effect of 4 to 6 hours, and duration of action of more than 12 hours. Very small doses will

have an earlier peak effect and shorter duration of action, while higher doses will have a longer time to peak effect and prolonged duration.

Pre-Mixed Insulin

Includes

- Humulin 70/30
- Novolin 70/30
- Novolog 70/30
- Humulin 50/50
- Humolog mix 75/25

which is NPH pre-mixed with either regular human insulin or a rapid- acting insulin analog. The insulin action profile is a combination of the short and intermediate acting insulins.

Long-acting insulin:

- Is absorbed slowly, has a minimal peak effect, and a stable plateau effect that lasts most of the day.
- Is used to control the blood sugar overnight, while fasting and between meals

Includes:

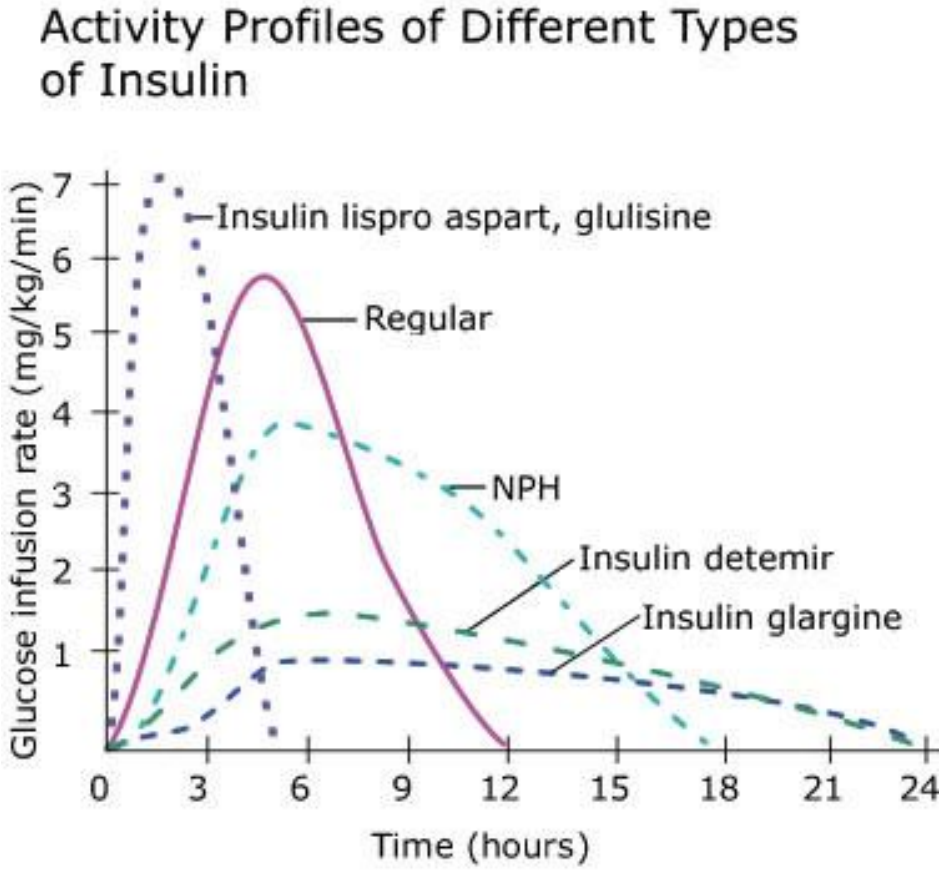
Long acting insulin analogs (Insulin Glargine, Insulin Detemir) which have an onset of insulin effect in 1 1/2-2 hours. The insulin effect plateaus over the next few hours and is followed by a relatively flat duration of action that lasts 12-24 hours for insulin detemir and 24 hours for insulin glargine.

Ultralong-acting insulin analogue

Insulin degludec (INN/USAN) is an ultralong-acting basal insulin analogue that was developed by Novo Nordisk under the brand name Tresiba. It is administered via subcutaneous injection once daily to help control the blood sugar level of those with diabetes. It has a duration of action that lasts up to 40 hours (compared to 18 to 26

hours provided by other marketed long-acting insulins such as insulin glargine and insulin detemir), making insulin degludec a once-daily basal insulin for all patients.

Figure 4



2.4 MISCELLANEOUS DRUGS

Antiparkinsonian Agents - Dopamine Agonists:

Quick-release bromocriptine acts on circadian neuronal activities within the hypothalamus to reset the abnormally elevated hypothalamic drive for increased plasma glucose, triglyceride, and free fatty acid levels in fasting and postprandial states in patients with insulin resistance.

Bromocriptine (Cycloset®)This quick- release formulation is the only bromocriptine product indicated for type 2 diabetes mellitus. It is indicated as an adjunct to diet and exercise to improve glycemic control.

3. BLOOD GLUCOSE PARAMETERS [36,37,38]

a. Glycated Hemoglobin (HbA1c)

Glycated hemoglobin (glycosylated hemoglobin, hemoglobin A1c, HbA1C, A1C, or Hb_1c; sometimes also HbA1c) is a form of hemoglobin used primarily to identify the average plasma glucose concentration over prolonged periods of time. It is formed in a non-enzymatic glycation pathway by hemoglobin's exposure to plasma glucose. Normal levels of glucose produce a normal amount of glycated hemoglobin. As the average amount of plasma glucose increases, the fraction of glycated hemoglobin increases in a predictable way. This serves as a marker for average blood glucose levels over the previous months prior to the measurement.

The red blood cells of all individuals contain hemoglobin, which is responsible for carrying oxygen through the bloodstream. When hemoglobin combines with glucose (sugar), a molecule called glycosylated hemoglobin, or Hemoglobin A1c (HbA1c), is formed. Since everyone has glucose in their blood, all individuals also have glycosylated hemoglobin in their blood (usually between 3 and 5 percent of blood).

The amount of A1c in red blood cells is proportional to the amount or concentration of glucose in the blood, and to the age of the red blood cells. (The average red blood cell lives approximately 120 days, with new ones replacing dying red blood cells continuously. Accordingly, healthy individuals have a mixture of "young" and "old" red blood cells at all times.)

If an individual has high blood-sugar levels, such as exists in poorly controlled or untreated diabetes mellitus, the glycosylated hemoglobin percentage will be elevated. Since it is also related to the "age" of the red blood cells, the glycosylated hemoglobin percentage will correspond to the average glucose level over the previous two to three months. This average level is in contrast to a routine measurement of the blood-sugar level, which reflects any food intake over the previous twelve hours.

Clinical Usefulness

In diabetes mellitus, the blood sugar is elevated in the fasting state, with levels exceeding 126 milligrams per deciliter (mg/dL). Persistently elevated blood-glucose levels result in many chronic complications, such as kidney failure, blindness, and poor circulation in the legs, which can result in amputation.

Underlying Principle:

In the normal 120-day lifespan of the red blood cell, glucose molecules react with hemoglobin, forming glycated hemoglobin. In individuals with poorly controlled diabetes, the quantities of these glycated hemoglobins are much higher than in healthy people.

Once a hemoglobin molecule is glycated, it remains that way. A buildup of glycated hemoglobin within the zed cell, therefore, reflects the average level of glucose to which the cell has been exposed during its life-cycle. Measuring glycated hemoglobin assesses the effectiveness of therapy by monitoring long term serum glucose regulation. The HbA1c level is proportional to average blood glucose concentration over the previous four weeks to three months. Some researchers state that the major proportion of its value is related to a rather shorter period of two to four weeks.

The 2010 American Diabetes Association Standards of Medical Care in Diabetes added the A1c> 6.5% as another criterion for the diagnosis of diabetes, but this is controversial and has not been universally adopted.

The chart below shows the average daily blood glucose levels for four different HbA1c values. HbA1c Value averages daily blood glucose level over past three months.

Table 5

Normal values of HbA1c

Result	A1c
Normal	< 5.7%
Prediabetes	5.7% to 6.4%
Diabetes	>6.5%

The HbA1c test should be done every three to six months, depending on the patient's treatment program and level of control. It's a good idea to discuss the HbA1c test with your doctor or diabetes educator, then, when you find out your HbA1cvalue, you'll know whether you are on target, or whether you need to work with your physician or diabetes educator on better control of your diabetes.

b. Fasting Plasma Glucose (FPG)

This test checks the patient's fasting blood glucose levels. Fasting means after not having anything to eat or drink (except water) for at least 8 hours before the test. This test is usually done first thing in the morning, before breakfast.

Diabetes is diagnosed at fasting blood glucose of greater than or equal to 126 mg/dL

Table 6

Normal values of Fasting Plasma Glucose

Result	Fasting Plasma Glucose (FPG)
Normal	less than 100 mg/dL
Prediabetes	100 mg/dL to 125 mg/dL
Diabetes	126 mg/dL or higher

c. Oral Glucose Tolerance Test (also called the OGTT)

The OGTT is a two-hour test that checks your blood glucose levels before and 2 hours after you drink a special sweet drink. It tells the doctor how your body processes glucose.

Diabetes is diagnosed at 2 hour blood glucose of greater than or equal to 200 mg/dL

Table 7

Normal values of Oral Glucose Tolerance Test

Result	Oral Glucose Tolerance Test (OGTT)
Normal	less than 140 mg/dl
Prediabetes	140 mg/dl to 199 mg/dl
Diabetes	200 mg/dl or higher

d. Random (also called Casual) Plasma Glucose Test

This test is a blood check at any time of the day when you have severe diabetes symptoms.

Diabetes is diagnosed at blood glucose of greater than or equal to 200 mg/dL

4. BODY MASS INDEX [32-35]

The body mass index (BMI), or Quetelet index, is a heuristic proxy for human body fat based on an individual's weight and height. BMI does not actually measure the percentage of body weight. It was invented between 1830 and 1850 by the Belgian polymath Adolph quetelet during the course of developing "social physics". Body mass index is defined as the individual's body weight divided by the square of his or her height. The formulae universally used in medicine produce a unit of measure of kg/m^2.

The healthy weight range is based on a measurement known as the body mass index (BMI).this can be determined by using weight and height of a person.

BMI can be used to indicate if the patients are overweight, obese, underweight or normal. It will, however, over estimate fatness in people who are muscular or athletics Scientists and researchers have found the BMI to be a valuable tool in the study of obesity, diabetes and heart disease. Early diagnosis of a poor BMI can potentially aid in the prevention of disease and provide advanced warning of any health problem.

Body mass index (BMI) is one of the most accurate ways to determine when extra pounds translate into health risks. BMI is a measure which takes into account a person's weight and height to gauge total body fat in adults. Someone with a BMI of 26 to 27 is about 20 present over weight, which is generally believed to carry moderate health risks. A BMI of 30 and higher is considered obese. The higher the BMI, the greater the risk of developing additional health problems.

Obesity and diabetes:

Diabetes is spreading worldwide as an epidemic. Diabetes is a disorder in which the body cells fail to take up glucose from the blood. Wasting of tissues is seen as glucose-starved cells are forced to consume their own proteins. Diabetes is the cause for blindness, kidney failure and amputation in adults. Individuals with diabetes lack the ability to use the hormone insulin.

As we start eating food, our body starts producing insulin. The insulin signal attaches to a special receptor on the cell surface, to make the cell turn-on its own glucose transporting machinery. It had been observed that type 2 diabetics have normal or even elevated levels of insulin in their body with normal insulin receptor but, due to some unknown reason, the binding of insulin to the cell receptors does not starts the glucose transporting machinery, which it is supposed to do. Special proteins called IRS (insulin receptor substrate) are inside the cell. In type 2 diabetes something is interfering with the action of the IRS protein and it is also estimated that about 80% of those who develop type 2 diabetes are obese. When insulin attaches to the receptor protein, the receptor responds by adding a chemical called a phosphate group onto the IRS molecules due to which the IRS molecules turn into action. Once activated, they start variety of processes, including an enzyme that turns on the glucose transporter machinery.

Overweight and obesity are both labels for series of weight, greater than what is generally considered healthy for an individual. BMI ranges for children and teens above a normal weight have different labels (at risk of overweight and overweight). Excess body weight is implicated as a risk factor for many disorders including heart disease, cancer, diabetes, female infertility, prostate enlargement, uterine fibroids, gallstone and gestational diabetes etc. The location of fat deposits in the body leads to different risks associated with it. Increased abdominal fat can be estimated by waist size. Dozens of controlled clinical trials were carried out to determine the effect of weight loss on fasting blood glucose. They found:

- ✓ Weight loss produced by lifestyle modification declines blood glucose levels and HbA1c in type 2 diabetis.
- ✓ Glucose tolerance can be improved in overweight individuals by decreasing abdominal fat.
- ✓ Glucose tolerance can also be improved in overweight individuals with increased cardio respiratory fitness.

In 1995, the U.S. national institute of health and the American health foundation issued new guidelines that define healthy weight as a BMI below 25.

Table 8

Weight status	Body mass index in Kg/ m^2
Underweight	17-18.4
Normal	18.5-24.9
Overweight	25.0-29.9
Obese class1	30.0 -34.9
Obese class II	35-39.9
Obese class III	> 40

Calculation of BMI:

Using following formula to find **BMI**

$$\textbf{BMI} = \frac{\text{Mass (kg)}}{\text{Height (m)}^2}$$

Table 9

S.NO	WEIGHT STATUS	WOMEN	MEN
1	Anorexia	< 17.5	< 17.5
2	Under weight	< 19.1	< 20.7
3	In normal range	19.1-25.8	20.7-26.4
4	Marginally overweight	25.8-27.3	26.4-27.8
5	Over weight	27.3-32.3	27.8-31.1
6	Very over weight or Obese	>32.3	>31.1
7	Severely obese	35-40	35-40
8	Morbidly obese	40-50	40-50
9	Super obese	50-60	50-60

5. DRUG PROFILE [39-46]

1. METFORMIN[39]

General description:

Metformin is an oral antidiabetic drug in the biguanide class. It is the firstline drug of choice for the treatment of type 2 diabetes.

Chemical data

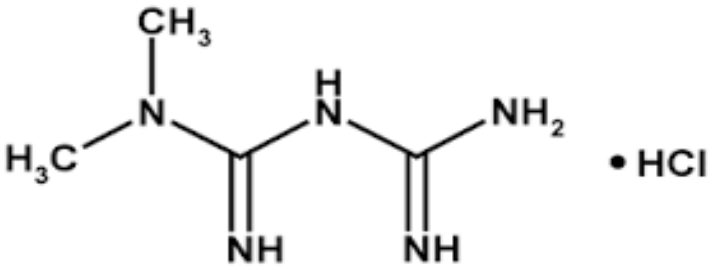
ChemicalFormula : $C_4H_{11}N_5$

Molecular Mass : 129.164 g/mol(free)

165.63 g/mol(HCL)

Chemical Name : N,N-dimethylimido dicarbonimidicdiamide

Chemical structure:



Metformin Hydrochloride

Mechanism of action

Metformin improves hyperglycemia primarily through its suppression of hepatic glucose production (hepatic gluconeogenesis) the average person with type 2 diabetes has three times the normal rate of gluconeogenesis metformin treatment reduces this by over one third. Metformin activates AMP-activated protein kinase (AMPK),a liver enzyme that plays an important role in insulin signaling, whole body energy balance, and the metabolism of glucose and fats ; activation of AMPK is required for metfomin's inhibitory effect on the production of glucose by liver cells. Research published in 2008 further elucidated metformin's mechanism of action, showing that activation of AMPK is required for an increase in the expression of SHP, which in turn inhibits the expression of the hepatic gluconeogenic genes PEPCK and Glc-6-Pase.metformin is frequently used in research along with AICAR as an AMPK agonist. The mechanism by which biguanides increase the activity of AMPK remains uncertain; however, research suggests that metformin increases the amount of cystolic AMP (as opposed to a change in total AMP or total AMP/ATP)

In addition to suppressing hepatic glucose production, metformin increases insulin sensitivity, enhances peripheral glucose uptake (by phosphorylating GLUT-4 enhancer factor), increases fatty acid oxidation. and decreases absorption of glucose from the gastrointestinal tract. Increased peripheral utilization of glucose may be due to improved insulin binding to insulin receptors.

Pharmacokinetics;

Absorption:

Metformin has an oral bioavailability of 50-60% under fasting conditions, and is absorbed slowly.

Distribution:

Peak plasma concentrations (C_{max}) are reached within one to three hours of taking immediate-release metformin and four to eight hours with extended-release formulations. The plasma protein binding of metformin is negligible, as reflected by its very high apparent volume of distribution (300-1000 L after a single dose). Steady state is usually reached in one or two days.

Metabolism:

Metformin is not metabolized. It is cleared from the body by tubular secretion and excreted unchanged in the urine; metformin is undetectable in blood plasma within 24 hours of a single oral dose.

Excretion:

The average elimination half life in plasma is 6.2 hours. Metformin is distributed to (and appears to accumulate in) red blood cells, with a much longer elimination half-life: 17.6 hours.

Contraindications :

Metformin is contraindicated in patients with:

1) Renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ≥1.5 mg/dL [males], ≥1.4 mg/dL [females] or abnormal creatinine clearance), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia.
2) Congestive heart failure requiring pharmacologic treatment.
3) Known hypersensitivity to metformin hydrochloride.
4) Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

Metformin should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function.

Drug Interactions

Glyburide

The influence of glyburide on metformin pharmacokinetics was assessed in a single-dose interaction study in healthy subjects. Co-administration of a single dose of 500 mg metformin and 5 mg glyburide did not result in any changes in metformin

pharmacokinetics as AUC, C_{max} as well as T_{max} were unchanged. Changes in Pharmacodynamic were not evaluated in this study.

Furosemide

A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration. Furosemide increased the metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of furosemide were 31 % and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when co-administered chronically.

Nifedipine

A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that co-administration of nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. T_{max} and half-life were unaffected. Nifedipineappears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Cationic drugs

Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or Vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose, metformin-cimetidine drug interaction studies, with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics.

Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of metformin and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Others

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, cA1cium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving metformin, the patient should be closely observed for loss of blood glucose control. When such drugs are withdrawn from a patient receiving metformin, the patient should be observed closely for hypoglycemia. In healthy volunteers, the pharmacokinetics of metformin and propranolol, and metformin and ibuprofen were not affected when co-administered in single-dose interaction studies. Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to the sulfonylurea, which are extensive.

Adverse effects

The most common adverse effect of motorman is gastrointestinal upset, including diarrhea, cramps, nausea, vomiting and increased flatulence; motormanis more commonly associated with gastrointestinal side effects than most other anti-diabetic drugs. The most serious potential side effect of motorman use is lactic acidosis; this complication is very rare, and the vast majority of these cases seems to be related to co morbid conditions such as impaired liver or kidney function, rather than to the motorman itself.

Motorman has also been reported to decrease the blood levels of thyroid stimulating hormones in patients with hypothyroidism and, in men, luteinizing hormone and testosterone. The clinical significance of these changes is still unknown.

2. Glimepiride[40]

Class : Antidiabetic agent

General Description

Glimepiride is used for the treatment of diabetes mellitus type 2.

Mechanism of action

The primary mechanism of action of AMARYL® (glimepiride) in lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells. In addition, extra-pancreatic effects may also play a role in the activity of glimepiride. This is supported by both preclinical and clinical studies demonstrating that glimepiride administration can lead to increased sensitivity of peripheral tissues to insulin. However, the mechanism by which glimepiride lowers blood glucose during long-term administration has not been clearly established.

Chemical data

Proper name : Glimepiride

Chemical name :1-[{p-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1carboxamido)ethyl]phenyl}sulfonyl]-3-(trans-4methylcyclohexyl)urea

Molecular formula and molecular mass: $C_{24}H_{34}N_4O_5S$ 490.62

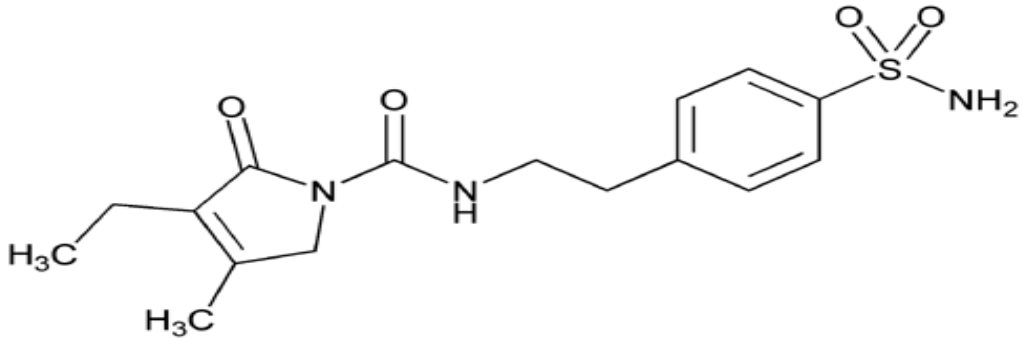
Physicochemical properties: Glimepiride is a white to yellowish-white, crystalline, odorless to practically odorless powder.

Glimepiride is practically insoluble in water.

pKa values: 6.2 ± 0.1 at 37°C

Melting point: 207°C

Chemical structure



Pharmacokinetics

Absorption:

After oral administration, glimepiride is completely (100%) absorbed from the GI tract. Studies with single oral doses in normal subjects and with multiple oral doses in patients with type 2 diabetes have shown significant absorption of glimepiride within 1 hour after administration and peak drug levels (Cmax) at 2 to 3 hours.

Distribution:

After intravenous dosing in normal subjects, the volume of distribution (V_d) was 8.8 L (113 ml/kg), and the total body clearance (CL) was 47.8 mL/min. Protein binding was greater than 99.5%.

Metabolism:

Glimepiride is completely metabolized by oxidative biotransformation after either IV or oral administration. The major metabolites are the cyclohexylhydroxy methyl derivative (M1) and the carboxyl derivative (M2).

Excretion:

When 14C-glimepiride was given as a single dose orally, approximately 60% of the total radioactivity was recovered in the urine in 7 days and metabolites M1 (predominant) and M2 accounted for 80-90% of that recovered in the urine.

Approximately 40% of the total radioactivity was recovered in feces and metabolites M1 and M2 (predominant) accounted for about 70.

Special Populations and Conditions

Pediatrics: No studies were performed in pediatric patients.

Geriatrics: There were no significant differences in glimepiride pharmacokinetics between the two age groups. The mean AUC at steady state for the older patients was about 13% lower than that for the younger patients.

Gender: There were no differences between males and females in the pharmacokinetics of glimepiride when adjusting for differences in body weight.

Race: No pharmacokinetic studies to assess the effects of race have been performed.

Hepatic Insufficiency: No studies were performed in patients with hepatic insufficiency.

Pregnant Women: There are no adequate and well-controlled studies in pregnant women.

Renal Insufficiency: Mean urinary excretion of metabolites M1 plus M2 as percent of dose, however, decreased (44.4%, 21.9%, and 9.3%).

Indication and usage

Glimepiride is indicated as an adjunct to proper dietary management, exercise and weight reduction to lower the blood glucose in patients with type 2 diabetes whose hyperglycemia cannot be controlled by diet and exercise alone. It may be used in combination with metformin when diet and exercise. It is also indicated for use in combination with insulin to lower blood glucose in patients with type 2 diabetes whose hyperglycemia cannot be controlled by diet and exercise in conjunction with an oral hypoglycemic agent alone.

Dosage and Administration

Usual Starting Dose

The usual starting dose of glimepiride as initial therapy is 1 mg once daily, administered with breakfast or the first main meal.

Metformin Combination Therapy

Combination therapy with glimepiride and metformin may be used in patients who do not respond adequately to the maximal dose of glimepiride or in secondary failure patients.

Insulin Combination Therapy

Combination therapy with glimepiride and insulin may be used in secondary failure patients. The recommended glimepiride dose is 8 mg once daily administered with the first main meal. After starting with low-dose insulin, upward adjustments of insulin can be done approximately weekly as guided by frequent measurements of fasting blood glucose.

Storage and Stability

Store between 15°C and 30°C. Dispense in well-closed container.

Drug Interactions

The hypoglycemic action of sulfonylureas may be potentiated by certain drugs, including anabolic steroids and male sex hormones, ACE inhibitors, insulin and other oral antidiabetics, nonsteroidal anti-inflammatory drugs and other drugs that are highly protein bound, such as azapropazone, sulfonamides (e.g. sulphaphenazole), chloramphenicol, clarithromycin, coumarins, cyclophosphamide, disopyramide, fenyramidol, fenfluramine, fibrates, fluconazole, fluoxetine, guanethidine, ifosfamide, miconazole, monoamine oxidase inhibitors, oxyphenbutazone, paraaminosalicylicacid, pentoxifylline (high dose parenteral), phenylbutazone, probenecid, propranolol, quinolones, salicylates, sulfonamide antibiotics, sulfinpyrazone, and tetracycline.

Adverse reactions

Body as a whole: abdominal pain, laboratory test abnormal, and pain in extremity

Cardiovascular: palpitation and vasodilation

Digestive: diarrhea, increased appetite, dyspepsia, anorexia, and gastrointestinal pain

Metabolic and Nutritional Disorders: hypoglycemic reaction and hyperglycemia

Nervous system: tremor, insomnia, sweating increased, nervousness, dry mouth, hot flashes, and paresthesia

Skin and appendages: pruritus and urticaria

Special Senses: blurred vision

Urogenital System: increased urinary frequency and nocturia

Warning

Over a period of time, patients may become progressively less responsive to therapy with oral hypoglycemic agents because of deterioration of their diabetic state.

3. Gliclazide[40]

Class: Antidiabetic agent

General Description : Gliclazide is used for the treatment of type 2 diabetes mellitus .

Mechanism of action

Gliclazide is a hypoglycemic agent of the sulfonylurea group. The hypoglycemic action of gliclazide is related to an improvement in insulin secretion from the functioning beta cells of the pancreas. It potentiates the insulin release, improves the dynamics of insulin. Increase in postprandial insulin and C-peptide secretion persists after two years of treatment. Gliclazide has extra-pancreatic actions. These metabolic actions are accompanied by hemovascular effects. However, the mechanism of action

regarding these effects is still poorly understood. The clinical significance of these effects has not been established.

Chemical Data

Proper name : gliclazide

Chemical name :1-(hexahydrocyclopenta[c]pyrrol-2(1H)-yl)-3-[(4methylphenyl)sulphonyl]urea (European Pharmacopoeia)

Molecular formula: $C_{15}H_{21}N_3O_3S$

Molecular mass : 323.4

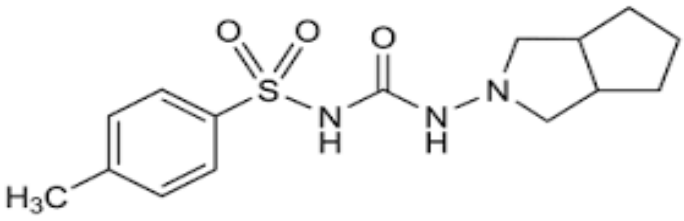
Physicochemical properties:

Appearance: white or almost white powder.

Solubility: practically insoluble in water freely soluble in methylene chloride sparingly soluble in acetone slightly soluble in ethanol 96%. Acid function **pKa:** 5.6 Overall distribution coefficient of gliclazide between water and octanol at pH 7.4 (Log D pH 7.4) is 0.4

Melting point: Approximately 168°C

Chemical structure



Pharmacokinetics

Absorption: Gliclazide is slowly and completely absorbed from the gastro-intestinal tract (mean absolute bioavailability of 97%). After administration, plasma concentrations rise gradually and the maximum concentration is usually reached after about 6 hours, with a plateau maintained for another 4 to 6 hours.

Distribution

A single daily dose maintains effective gliclazide plasma concentrations over 24 hours.

Metabolism

Although more than 90% of unchanged gliclazide is found in plasma following oral administration, this is extensively metabolized with little of the unchanged compound (<1%) found in urine. Six principal metabolites have been identified in urine, essentially oxidized and hydroxylated derivatives, and two glucurono conjugates. No active metabolites have been detected in plasma.

Excretion

Gliclazide metabolites and conjugates are primarily (60-70%) eliminated via the urine, with about 10 to 20% elimination via feces. The mean elimination half life is 16 h (range 12-20 h).

Special Populations and Conditions

Pediatrics: Safety and effectiveness of gliclazide in children have not been established,therefore not recommended for use in children and adolescents.

Geriatrics: No clinically significant modifications in the pharmacokinetic parameters have been observed in elderly patients.

Gender: No significant relationship was found between any of the pharmacokinetic parameters and the covariates gender, body weight and creatinine clearance.

Dosage and Administration

The daily dose of gliclazide may vary from 30 to 120 mg once daily (i.e., one half tablet to 2 tablets of gliclazide 60 mg, or 1 to 4 tablets of gliclazide 30 mg).

A single daily dose provides effective blood glucose control. The single daily dose may be between 30 mg and 90 mg, or even 120 mg. The daily dose should not exceed 120 mg.

Dose adjustment should be carried out in steps of 30 mg, according to the blood glucose response. Each step should last for at least two weeks.

Contraindication

The concomitant use of miconazole and gliclazide is contraindicated.

Pregnant Women: Gliclazide is contraindicated in pregnancy. It is recommended that insulin be used during pregnancy in diabetic women.

Drug Interaction

As a result of drug interaction, hypoglycemia may be potentiated when a sulfonylurea is used concurrently with agents such as: long-acting sulfonamides, tuberculostatics, NSAIDs, fibrates, monoamine oxidase inhibitors, salicylates, probenecid, beta-blockers, azole antifungal agents (oral and parenteral preparations), H2 receptor antagonists, angiotensin converting enzyme inhibitors and clarithromycin. In addition, while not approved for use with other antidiabetic agents, hypoglycaemia is potentiated when gliclazide is used in combination with other antidiabetic agents.

Barbiturates should be used with caution in patients receiving an oral hypoglycemic agent since they may reduce the hypoglycemic effect.

Sulfonylureas may potentiate the action of anticoagulants**.**

Adverse Reactions

The most frequent adverse drug reactions are hypoglycaemia and gastrointestinal disturbances (including abdominal pain, nausea, vomiting, dyspepsia, diarrhea, constipation).

Serious adverse drug reactions during clinical trials were malaise, acute renal failure, and thrombophlebitis

Storage and Stability

Store at room temperature (15°C-30°C). Keep out of reach of children and pets. Unused medication should not be disposed of down the drain or in household garbage.

Warnings and Precautions

Periodic assessment of cardiovascular, ophthalmic, renal and hepatic status is advisable. Since the effects of oral hypoglycemic agents on the vascular changes and other long-term sequelae of diabetes mellitus are not fully known, patients receiving such drugs must be closely observed for both short- and long-term complications.

4.Canagliflozin[41,42,43]

Class: SGLT2 inhibitors

General Description: It is an oral hypoglycemic drug used in the treatment of type2 diabetes mellitus.

Mechanism of Action

Sodium-glucose co-transporter 2 (SGLT2), expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. Canagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, canagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose (RTG), and thereby increases urinary glucose excretion (UGE).

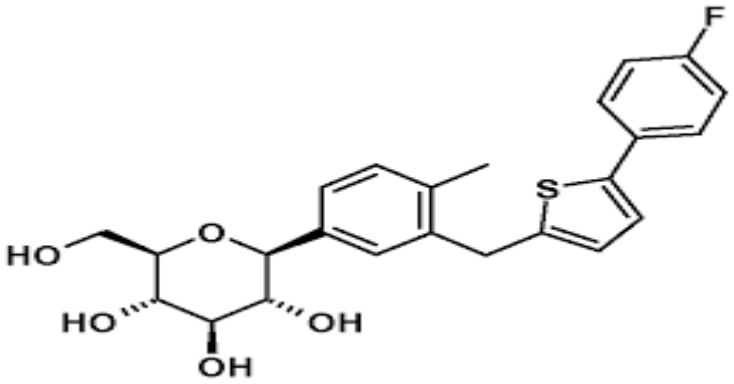
Chemical Data

Chemical Formula: $C_{24}H_{25}FO_5S•1/2\ H2O$

Chemicalname:(1S)-1,5-anhydro-1-[3-[[5(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl]-D-glucitol hemihydrate

molecular weight: 453.53

Chemical Structure



Pharmacokinetics

The pharmacokinetics of canagliflozin is similar in healthy subjects and patients with type 2 diabetes.

Absorption

The mean absolute oral bioavailability of canagliflozin is approximately 65%.

Plasma Cmax and AUC of canagliflozin increased in a dose-proportional manner from 50 mg to 300 mg. The apparent terminal half-life (t1/2) was 10.6 hours and 13.1 hours for the 100 mg and 300 mg doses, respectively. Steady-state was reached after 4 to 5 days of once-daily dosing with canagliflozin 100 mg to 300 mg.

Distribution

The mean steady-state volume of distribution of canagliflozin following a single intravenous infusion in healthy subjects was 83.5 L, suggesting extensive tissue distribution. Canagliflozin is extensively bound to proteins in plasma (99%), mainly to albumin.

Metabolism

O-glucuronidation is the major metabolic elimination pathway for canagliflozin, which is mainly glucuronidated by UGT1A9 and UGT2B4 to two inactive O-glucuronide metabolites.

Excretion

Mean systemic clearance of canagliflozin was approximately 192 mL/min in healthy subjects following intravenous administration.

Specific Populations

Renal Impairment

Renal impairment did not affect the $C_{max}$of canagliflozin. The pharmacodynamic response to canagliflozin declines with increasing severity of renal impairment. Canagliflozin was negligibly removed by hemodialysis.

Hepatic Impairment

Relative to subjects with normal hepatic function, the geometric mean ratios for Cmax and AUC∞ of canagliflozin were 107% and 110%, respectively, in subjects with Child-Pugh class A (mild hepatic impairment) and 96% and 111%, respectively, in subjects with Child-Pugh class B (moderate hepatic impairment) following administration of a single 300 mg dose of canagliflozin.

Combination Therapy

Add-on Combination Therapy with Metformin

Canagliflozin 100 mg and 300 mg once daily also resulted in a greater proportion of patients achieving an HbA1c less than 7%, in significant reduction in fasting plasma glucose (FPG), in improved postprandial glucose (PPG), and in percent body weight reduction compared to placebo when added to metformin.

Adverse Reactions

The following important adverse reactions are:

- Hypotension
- Ketoacidosis
- Acute Kidney Injury and Impairment in Renal Function

• Hyperkalemia

• Urosepsis and Pyelonephritis

• Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

• Genital Mycotic Infections

• Hypersensitivity Reactions

• Bone Fracture

• Increases in Low-Density Lipoprotein (LDL-C)

Dosage and Administration

• The recommended starting dose is 100 mg once daily, taken before the first meal of the day.

• Dose can be increased to 300 mg once daily in patients tolerating canagliflozin100 mg once daily who have an eGFR of 60 mL/min/1.73 m^2 or greater and require additional glycemic control.

• Assess renal function before initiating and periodically thereafter.

• Limit the dose of canagliflozin to 100 mg once daily in patients who have an eGFR of 45 to less than 60 mL/min/1.73 m^2

• Initiation or use of canagliflozin is not recommended if eGFR is below 45 mL/min/1.73 m^2

Dosage Forms and Strengths

100 mg, 300 mg

Storage and Handling

Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F).

Warnings and Precautions

Hypotension: Before initiating canagliflozin assess volume status and correct hypovolemia in patients with renal impairment, the elderly, in patients with low systolic blood pressure, or if on diuretics, ACEi, or ARB. Monitor for signs and symptoms during therapy

Ketoacidosis: Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level.

Acute kidney injury and impairment in renal function: Consider temporarily discontinuing in settings of reduced oral intake or fluid losses. If acute kidney injury occurs, discontinue and promptly treat. Monitor renal function during therapy.

Hyperkalemia: Monitor potassium levels in patients with impaired renal function and in patients predisposed to hyperkalemia

Urosepsis and Pyelonephritis: Evaluate patients for signs and symptoms of urinary tract infections and treat promptly

Hypoglycemia: Consider a lower dose of insulin or the insulin secretagogue to reduce the risk of hypoglycemia when used in combination with canagliflozin.

Genital mycotic infections: Monitor and treat if indicated.

Hypersensitivity reactions: Discontinue canagliflozin and monitor until signs and symptoms resolve.

Bone fracture: Consider factors that contribute to fracture risk before initiating canagliflozin

Increased LDL-C: Monitor LDL-C and treat if appropriate.

5. Dapagliflozin[46]

Class: SGLT2 inhibitors

General Description: It is an oral hypoglycemic drug used in the treatment of type2 diabetes mellitus.

Mechanism of Action

Dapagliflozin is a reversible inhibitor of sodium-glucose co-transporter 2 (SGLT2) that improves glycemic control in patients with type 2 diabetes mellitus by reducing renal glucose reabsorption leading to urinary excretion of excess glucose (glucuresis). SGLT2 is selectively expressed in the kidney. SGLT2 is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Dapagliflozin improves both fasting and post-prandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary excretion of excess glucose. The amount of glucose removed by the kidney through this mechanism is dependent upon the blood glucose concentration and GFR. Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycemia.

Dapagliflozin acts independently of insulin secretion and insulin action. Urinary glucose excretion (glucuresis) induced by dapagliflozin is associated with caloric loss and reduction in weight. Inhibition of glucose and sodium co-transport by dapagliflozin is also associated with mild diuresis and transient natriuresis. Dapagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is greater than 1400 times more selective for SGLT2 vs. SGLT1, the major transporter in the gut responsible for glucose absorption.

Chemical Data

Common Name: Dapagliflozinpropanediol monohydrate

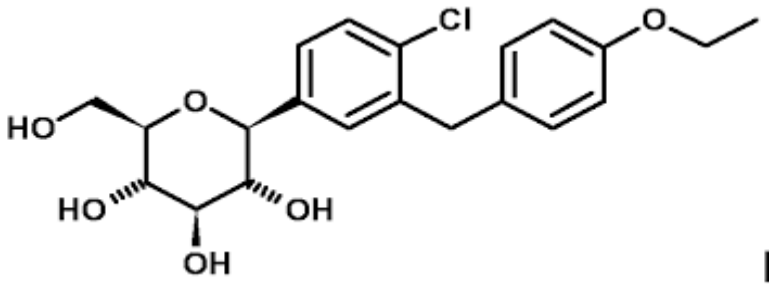
Chemical Name: D-glucitol,1,5-anhydro-1-C-[4-chloro-3-[(4ethoxyphenyl)methyl]phenyl]-, (1S)-,compd. with (2S)-1,2-propanediol, hydrate (1:1:1)

Molecular Formula: $C_{21}H_{25}ClO_6 \bullet C_3H_8O_2 \bullet H_2O$

Molecular mass: 502.98; 408.87

Physicochemical Properties: Dapagliflozin propanediol is a white to off-white non-hygroscopic crystalline powder. It is slightly soluble in water, soluble in acetonitrile and freely soluble in acetone, ethanol, isopropanol, methanol and tetrahydrofuran.

Chemical Structure



Pharmacokinetics

Absorption: Dapagliflozin was rapidly and well absorbed after oral administration and can be administered with or without food. Geometric mean steady-state dapagliflozin Cmax and AUCτ values following once daily 10 mg doses of dapagliflozin were 158 ng/mL and 628 ng/mL, respectively. Maximum dapagliflozin plasma concentrations (Cmax) were usually attained within 2 hours after administration in the fasted state**.**

Distribution: Dapagliflozin is approximately 91% protein bound. Protein binding was not altered in various disease states (eg, renal or hepatic impairment).

Metabolism: The mean plasma terminal half-life (t1/2) for dapagliflozin was 12.9 hours.

Excretion: Dapagliflozin and related metabolites are primarily eliminated via urinary excretion, of which less than 2% is unchanged dapagliflozin.

Indications and Clinical Use

Monotherapy: Dapagliflozin is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus for whom metformin is inappropriate due to contraindications or intolerance.

Add-on combination: It is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with: • metformin, • a sulfonylurea, or • insulin (alone or with metformin) when the existing therapy, along with diet and exercise, does not provide adequate glycemic control.

Special Populations and Conditions

No dosage adjustments based on pharmacokinetic analyses are recommended for mild renal impairment, mild, moderate and severe hepatic impairment, age, gender, race and body weight.

Pediatrics (< 18 years of age): Pharmacokinetics in the pediatric and adolescent population have not been studied.

Drug Interactions

Dapagliflozin is unlikely to affect the pharmacokinetics of concurrently administered medications that are P-gp, OCT2, OAT1, or OAT3 substrates.

Drug-Drug Interactions Effect of other drugs on dapagliflozin

In studies conducted in healthy subjects, the pharmacokinetics of dapagliflozinare not altered by the co-administered drugs.

Adverse Reactions

The most commonly reported adverse events during treatment with FORXIGA 5 mg or 10 mg (≥5%) were female genital mycotic infections, nasopharyngitis and urinary tract infections.

Contraindications

Dapagliflozin is contraindicated in:

• Patients with a history of hypersensitivity reaction to the active substance or to any of the excipients.

• Patients with moderate to severe renal impairment, defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2, or end-stage renal disease [ESRD].

Monitoring and Laboratory Tests Renal function:

Renal function should be assessed prior to initiation of Dapagliflozin and regularly thereafter as it is contraindicated in patients with an eGFR<60 mL/min/1.73 m^2.

Reduced intravascular volume: Dapagliflozin is not recommended for use in patients who are volume depleted.

LDL-cholesterol: LDL-C levels should be monitored during treatment with dapagliflozin due to dose-dependent increases in LDL-C seen with therapy.

Special Populations

Pregnant Women: Dapagliflozin must not be used in pregnancy.

Nursing Women: Dapagliflozin must not be used by a nursing woman.

Pediatrics (< 18 years of age): Safety and effectiveness in pediatric patients have not been established, therefore should not be used in this population.

Geriatrics (≥ 65 years of age): Older patients are more likely to have impaired renal function.

Storage And Stability

Store at room temperature (15-30°C). Keep in a safe place out of reach of children.

6. Empagliflozin[44,45]

Class: SGLT2 inhibitor

General Description: It is an oral hypoglycemic drug used in the treatment of type2 diabetes mellitus.

Mechanism of Action

Sodium-glucose co-transporter 2 (SGLT2) is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Empagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, empagliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion.

Chemical Data

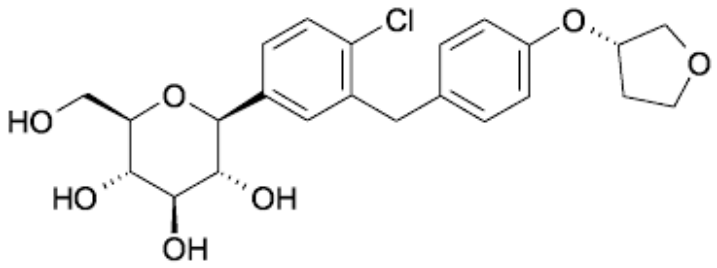
Common name: Empagliflozin

Chemical name: (1S)-1,5-anhydro-1-(4-chloro-3-{4-[(3S)-tetrahydrofuran-3 yloxy]benzyl}phenyl)-D-glucitol

Molecular formula: $C_{23}H_{27}ClO_7$

Molecular mass: 450.91 g/mol

Structural formula :



Physicochemical parameters:

Empagliflozin is a white to yellowish, not hygroscopic solid powder, very slightly soluble in water (0.28 mg/mL)

- sparingly soluble in methanol (33.4 mg/mL),
- slightly soluble in ethanol (8.0 mg/mL)

- slightly soluble in acetonitrile (2.6 mg/mL)
- slightly soluble in 50% methanol in water (6.4 mg/mL)
- soluble in 50% acetonitrile in water (68 mg/mL)
- practically insoluble in toluene (<0.001 mg/mL).

Pharmacokinetics

Absorption: After oral administration in patients with T2DM, empagliflozin was rapidly absorbed with peak plasma concentrations occurring at a median Tmax 1.5 h post-dose. Thereafter, plasma concentrations declined in a biphasic manner with a rapid distribution phase and a relatively slow terminal elimination phase.

Distribution: The apparent steady-state volume of distribution was estimated to be 73.8 L, based on a population pharmacokinetic analysis. Following administration of an oral [14C]-empagliflozin solution to healthy subjects, the red blood cell partitioning was approximately 36.8% and plasma protein binding was 86.2%, mainly to albumin.

Metabolism: No major metabolites of empagliflozin were detected in human plasma and the most abundant metabolites were three glucuronide conjugates (2-O-, 3-O-, and 6-O-glucuronide). Systemic exposure of each metabolite was less than 10% of total drug-related material.

Excretion: The apparent terminal elimination half-life of empagliflozin was estimated to be 12.4h and apparent oral clearance was 10.6 L/h based on the population pharmacokinetic analysis.

Indications and Clinical Use

Monotherapy

Empagliflozin is indicated for use as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus for whom metformin is inappropriate due to contraindications or intolerance.

Add-on combination: is indicated in adult patients with type 2 diabetes mellitus to improve glycemic control, when metformin used alone does not provide adequate glycemic control, in combination with:

• metformin,

• metformin and a sulfonylurea,

• pioglitazone (alone or with metformin),

• basal or prandial insulin (alone or with metformin),

when the existing therapy, along with diet and exercise, does not provide adequate glycemic control.

Special Populations and Conditions

Pediatrics (<18 years of age):

Studies characterizing the pharmacokinetics of empagliflozin in pediatric patients have not been performed.

Geriatrics (≥65 years of age):

Age did not have a clinically meaningful impact on the pharmacokinetics of empagliflozin based on the population pharmacokinetic analysis.

Body Mass Index: BMI had no clinically relevant effect on the pharmacokinetics of empagliflozin based on the population pharmacokinetic analysis.

Gender: Gender had no clinically relevant effect on the pharmacokinetics of empagliflozin based on the population pharmacokinetic analysis.

Race: Based on the population pharmacokinetic analysis, AUC was estimated to be 13.5% higher in Asian patients with a BMI of 25 kg/m^2 compared to non-Asian patients with a BMI of 25 kg/m^2. These changes are not considered clinically meaningful.

Hepatic Insufficiency: In subjects with mild, moderate, and severe hepatic impairment according to the Child-Pugh classification, AUC of empagliflozin increased approximately by 23%, 47%, and 75% and Cmax by approximately 4%,

23%, and 48%, respectively, compared to subjects with normal hepatic function. Experience in patients with severe hepatic impairment is limited.

Renal Insufficiency: In patients with mild (eGFR: 60 - <90 mL/min/1.73m^2), moderate (eGFR: 30 - <60 mL/min/1.73m^2), severe (eGFR: <30 mL/min/1.73m^2) renal impairment and patients with kidney failure/ESRD patients, AUC of empagliflozin increased by approximately 18%, 20%, 66%, and 48%, respectively, compared to subjects with normal renal function.

Monitoring and Laboratory Tests

Blood Glucose and HbA1c: Response to empagliflozin treatment should be monitored by periodic measurements of blood glucose and HbA1c levels.

Renal Function: Renal function should be assessed prior to initiation of empagliflozin and regularly thereafter, with more frequent monitoring in patients whose eGFR decreases to <60 mL/min/1.73m^2.

Reduced Intravascular Volume: Empagliflozin is not recommended for use in patients who are volume.Temporary interruption of treatment with JARDIANCE should be considered until fluid loss is corrected.

LDL-Cholesterol: LDL-cholesterol levels should be measured at baseline and at regular intervals during treatment with empagliflozin due to dose-dependent increases in LDL-C seen with therapy.

Adverse Reactions

- Genital Mycotic Infections
- Increased urination
- Urinary Tract Infections
- Volume Depletion and hypotension

WARNINGS AND PRECAUTIONS

General

Empagliflozin is not indicated for use in patients with type 1 diabetes and should not be used for the treatment of diabetic ketoacidosis.

Cardiovascular

Use in Patients at Risk for Volume Depletion, Hypotension and/or Electrolyte Imbalancesdue to its mechanism of action, Empagliflozin causes diuresis that may be associated with decreases in blood pressure.

Special Populations

Pregnant Women: must not be used in pregnancy.

Nursing Women: must not be used in nursing women.

Storage And Stability

Store at room temperature (15-30°C).

6. LITERATURE REVIEW

Wilding J. P. H *et al.,* in **2013** conducted a randomised double blind placebo – controlled phase 3 study evaluating the efficacy and safety of canagliflozin as on add-on to metformin plus sulphonyl urea in patients with N= 469 T2DM patients received canagliflozin 100 or 300 mg or placebo once daily during a 26-week core period and a 26 week extension. Prespecified primary end –point was change in HbA1c at 26 weeks and secondary end-points included change in HbA1c at 52 week as well as a proportion of patients achieving significant reduction in HbA1c with canagliflozin 100and 300mg vs placebo at week 26 and the reductions were maintained at week 52. Both canagliflozin doses reduced FPG and body weight vs placebo at week 26 and week 52. The study concluded that canagliflozin improved glycaemic control, reduced body weight, and was generally well tolerated in T2DM patients on metformin plus sulphonyl urea over 52 weeks.

Rong Qui *et al*., in **2014** evaluated the efficacy /safety of canagliflozin twice daily (BID)compared with placebo in patients with type 2 diabetes mellitus on metformin. An 18 week, randomised, double-blind, placebo controlled study with N=279 received canagliflozin 50 or 150 mg or placebo BID. The pre-specified primary end point was change from baseline in HbA1c at week 18 and the pre-specified secondary endpoints included proportion of patients reaching HbA1c <7.0%, change in FPG, and percent change in bodyweight , changes in systolic blood pressure and fasting plasma lipids were also evaluated and AEs were recorded throughout the study and noted that both the canagliflozin doses significantly lowered FPG and body weight and reduced systolic BP. The study concluded that canagliflozin 50 and 150 mg BID provided significant glycemic efficacy and bodyweight reduction and were generally well tolerated in patients with T2DM on background metformin.

Forst T *et al.,* in **2014** evaluated the efficacy and safety of canagliflozin in patients with T2DM inadequately controlled with metformin and pioglitazone in a randomised double blind, phase 3 study with patients N=342 received 100 or 300 mg during a 26 week placebo-controlled, core period and a 26 week active controlled extension in which placebo treated patients were switched to sitagliptin 100mg. The study revealed that canagliflozin 100 and 300 mg significantly lowered HbA1c compared with

placebo at week 26 and were maintained at week 52 . The study concluded that canagliflozin improved glycaemic control , reduced body weight and systolic BP and was generally well tolerated in patients with T2DM on metformin and pioglitazone over 52 weeks.

Lavalle Gonzalez F. J *et al.,* in **2013** aimed to evaluate the efficacy and safety of canagliflozinverses placebo and sitagliptin in patients with type 2 diabetes who were being treated with background metformin in a randomised, double blind , four arm parallel group consisting of N=1,284 with t2dm aged >18 and <80 years who had inadequate glycaemic control HbA1c >7.0%and <10.5% on metformin therapy received canagliflozin100 mg or 300mg, sitagliptin 100mg, or placebo (n=368,367,366,183, respectively) for a 26 week, placebo- and active controlled period followed by a 26 week , active controlled period (placebo group switched to sitagliptin). The primary endpoint was change from baseline in HbA1c at week 26 , secondary end points included changes in HbA1c (week 52) and FPG, body weight and systolic blood pressure (weeks 26 and 52) AEs were recorded throughout the study. The study concluded that canagliflozin improved glycaemia and reduced body weight vs placebo (week26) and sitagliptin (week 52) and was generally well tolerated in patients with T2DM on metformin.

Michael Nauck A *et al.,* in **2011**compared the efficacy, safety, and tolerability of dapagliflozin with the sulphonyl urea glipizide in patients with type 2 diabetes inadequately controlled with metformin monotherapy. A 52 week, double-blind multicentre, active-controlled, non-inferiority trial randomised patients with type 2 diabetes (baseline mean HbA1c 7.7%), who were receiving metformin monotherapy, to add-on dapagliflozin (n=406)or glipizide (n=408) up-titrated over 18 weeks , based on glycemic response and tolerability to <10 or <20 mg/day, respectively. The study concluded that dapagliflozin reduced weight and produced less hypoglycaemia than glipizide in type 2 diabetes inadequately controlled with metformin.

Ele Ferrannini *et al.,* in **2010** conducted a 24 week parallel group double blind placebo controlled phase 3 trial on dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycaemic control by diet and exercise with n=485 to receive once daily placebo or 2.5 ,5, 10 mg dapagliflozin once daily in the morning (main

cohort) or evening (exploratory cohort). The results showed mean A1c changes from baseline at week 24 were -0.23% with placebo and -0.58% , -0.77%, -0.89% with 2.5, 5, 10 mg dapagliflozin respectively. The study concluded that dapagliflozin lowered hyperglycaemia in treatment -naïve patients with newly diagnosed type 2 diabetes.

Alan Sinclair *et al.,* in **2014** evaluated the efficacy and safety of canagliflozin in patients with T2DM <65 and > 65yrs of age. A 26 week studies evaluating canagliflozin 100 and 300 mg were analyzed. efficacy evaluations included change from baseline in glycaemic parameters and systolic blood pressure and percent change from baseline in body weight, and percent change from baseline in fasting plasma lipids. Both canagliflozin doses reduced HbA1c, FPG , body weight and systolic BP relative to placebo in patients <65 and >65 years of age. Changes in lipid parameters with canagliflozin were similar in both age subsets. The study concluded that canagliflozin improved glycaemic control, body weight, and systolic BP, and was generally well tolerated in older patients with T2DM.

Min Chen *et al.,* in **2016** compared the effectiveness of sodium glucose co-transporter 2 inhibitors for controlling hyper glycaemia in patients with type 2 diabetes and a protocol for a systemic review and network meta-analysis were performed. The study examined effectiveness and safety of either canagliflozin , dapagliflozin, empagliflozin, ipragliflozin, tofogliflozin or luseogliflozin. The study was systematically retrieved in MEDLINE, EMBASE and the Cochrane Library, from the inception to November 2015. relative effectiveness and harms of the 6 SGLT2 inhibitors was demonstrated through this systemic review and network meta-analysis.

Schernthaner G *et al*., in **2013** evaluated the efficacy and safety of canagliflozin, a sodium glucose cotransporter 2 inhibitor, compared with sitagliptin in subjects with type 2 diabetes inadequately controlled with metformin plus sulfonylurea for 52-weeks, subjects using stable metformin plus sulfonylurea (N = 755) received canagliflozin 300 mg or sitagliptin 100 mg daily. At 52 weeks, canagliflozin 300 mg demonstrated non-inferiority and, in a subsequent assessment, showed superiority to sitagliptin 100 mg in reducing A1c (−1.03% [−11.3 mmol/mol] and −0.66% [−7.2 mmol/mol], respectively. Greater reductions in FPG, body weight, and systolic BP were observed with canagliflozin versus sitagliptin ($P < 0.001$).

Overall AE rates were similar with canagliflozin (76.7%) and sitagliptin (77.5%); incidence of serious AEs and AE-related discontinuations was low for both groups. Findings suggested that canagliflozin may be a new therapeutic tool providing better improvement in glycemic control and body weight reduction than sitagliptin, but with increased genital infections in subjects with type 2 diabetes using metformin plus sulfonylurea.

Cefalu W T *et al*., in **2013** compared the efficacy and safety of canagliflozin, an SGLT2 inhibitor, with glimepiride in patients with type 2 diabetes inadequately controlled with metformin.Patients aged 18–80 years with type 2 diabetes and glycatedhaemoglobin A1c (HbA1c) of 7·0–9·5% on stable metformin were randomly assigned and received canagliflozin 100 mg or 300 mg, or glimepiride (up-titrated to 6 mg or 8 mg per day) orally once daily. The primary endpoint was change in HbA1c from baseline to week 52, with a non-inferiority margin of 0·3% for the comparison of each canagliflozin dose with glimepiride.1450 of 1452 randomised patients received at least one dose of glimepiride (n=482), canagliflozin 100 mg (n=483), or canagliflozin 300 mg (n=485). For lowering of HbA1c at 52 weeks, canagliflozin 100 mg was non-inferior to glimepiride and canagliflozin 300 mg was superior to glimepiride.The study concluded that Canagliflozin provides greater HbA1c reduction than does glimepiride, and is well tolerated in patients with type 2 diabetes receiving metformin.

Bode B *et al*., in **2013** evaluated the efficacy and safety of canagliflozin therapy in older subjects (aged 55-80 years) with T2DM inadequately controlled on their current regimen of blood glucose-lowering agents. Subjects (N = 716) aged 55 to 80 years (mean, 63.6 years) with glycated hemoglobin (HbA1c) levels ≥ 7.0% to ≤ 10.0% were randomized and 714 received canagliflozin 100 mg or 300 mg or placebo (1:1:1) daily. At week 26, treatment with canagliflozin 100 mg and 300 mg significantly reduced HbA1c levels compared with placebo and both canagliflozin doses significantly reduced body weight, FPG level, and systolic BP, and increased HDL-C level compared with placebo. Canagliflozin improved glycemic control, reduced body weight and systolic BP, and was generally well tolerated in older subjects with T2DM who were on background therapy with a variety of blood glucose-lowering agents.

Devineni D *et al*., in **2012** observed a randomized, double-blind, placebo-controlled, parallel-group, 28-day study conducted at two sites, in 29 subjects with T2DM not optimally controlled on insulin and up to one oral antihyperglycaemic agent and the subjects were treated with canagliflozin 100 mg QD or 300 mg twice daily (BID) or placebo. Safety, tolerability, pharmacokinetic characteristics and pharmacodynamic effects of canagliflozin were examined. Glucose malabsorption following a 75-g oral glucose challenge was also examined and the results suggested that canagliflozin was well tolerated without evidence for glucose malabsorption, had pharmacokinetic characteristics consistent with once-daily dosing, and improved glycaemic control.

Bailey C J *et al*., in **2010** assessed the efficacy and safety of dapagliflozin in patients who have inadequate glycaemic control with metformin.546 adults with type 2 diabetes who were receiving daily metformin (>/=1500 mg per day) and had inadequate glycaemic control were randomly assigned to receive one of three doses of dapagliflozin (2.5 mg, n=137; 5 mg, n=137; or 10 mg, n=135) or placebo (n=137) orally once daily. The findings suggested that the addition of dapagliflozin to metformin provides a new therapeutic option for treatment of type 2 diabetes in patients who have inadequate glycaemic control with metformin alone.

Rosenstock J *et al*., in **2012** examined the safety and efficacy of dapagliflozin, a sodium-glucose cotransporter-2 inhibitor, added on to pioglitazone in type 2 diabetes inadequately controlled on pioglitazone.Treatment-naive patients or those receiving metformin, sulfonylurea, or thiazolidinedione entered a 10-week pioglitazone dose-optimization period with only pioglitazone. Patients receiving pioglitazone alone had greater weight gain (3 kg) than those receiving dapagliflozin plus pioglitazone (0.7–1.4 kg) at week 48. Dapagliflozin plus pioglitazone groups had less edema (2.1–4.3%) compared with placebo plus pioglitazone (6.5%); and congestive heart failure and fractures were rare. The results concluded that in patients with type 2 diabetes inadequately controlled on pioglitazone, the addition of dapagliflozin further reduced HbA1c levels and mitigated the pioglitazone-related weight gain without increasing hypoglycemia risk.

Hermansen K *et al*., in **2007** assessed the efficacy and safety of a 24-week treatment with sitagliptin, a highly selective once-daily oral dipeptidyl peptidase-4 (DPP-4) inhibitor, in patients with type 2 diabetes who had inadequate glycaemic control [glycosylated haemoglobin (HbA1c) >or=7.5% and <or=10.5%] while on glimepiride alone or in combination with metformin. Sitagliptin reduced HbA1c by 0.89% relative to placebo, compared with a reduction of 0.57% in the subset of patients on glimepiride alone. The addition of sitagliptin reduced FPG by 20.1 mg/dl ($p < 0.001$) and increased homeostasis model assessment-beta, a marker of beta-cell function. The results suggested that Sitagliptin 100 mg once daily significantly improved glycaemic control and beta-cell function in patients with type 2 diabetes who had inadequate glycaemic control with glimepiride or glimepiride plus metformin therapy.

7. NEED FOR THE PRESENT STUDY

Diabetes is fast gaining the status of a potential endemic in India with more than 62 million diabetic individuals currently diagnosed with the disease. India currently faces an uncertain future in relation to the potential burden that diabetes may impose upon our country.

The level of morbidity and mortality due to diabetes and its potential complications are enormous, and pose significant healthcare burdens on both families and society. Worryingly, diabetes is now being shown to be associated with a spectrum of complications and to be occurring at a relatively younger age within the country. In India, the steady migration of people from rural to urban areas, the economic boom, and corresponding change in life-style are all affecting the level of diabetes.

There are a number of challenges that plague diabetes care in India. Yet despite the increase in diabetes there remains a paucity of studies investigating the precise status of the disease because of the geographical, socio-economic, and ethnic nature of such a large and diverse country. Given the disease is now highly visible across all sections of society within India, there is now the demand for urgent research and intervention - at regional level - to try to mitigate the potentially catastrophic increase in diabetes that is predicted for the upcoming years.

8. AIM AND OBJECTIVE

AIM

To study the effectiveness of Sodium-Glucose Transport 2 Inhibitors (SGLT2 inhibitors) in patients with type 2 diabetes mellitus on the background treatment with metformin and a sulphonyl urea

OBJECTIVES

To assess the glycaemic control by observing:

- Fasting blood sugar
- Post-prandial blood sugar
- Glycosylated haemoglobin (HbA1c)
- Reduction in body weight

9. PLAN OF THE WORK

The Entire study was carried out for a period of nine months from November 2015 through July 2016. The proposal has been designed as shown below:

NOVEMBER – DECEMBER 2015

- Obtaining consent from the hospital authorities
- Survey of Literature
- Preparation of study design of data entry format (Proforma)
- Approval from institutional ethics committee (IEC)

JANUARY – JUNE 2016

- Selection of Patients according to Inclusion-exclusion criteria
- Obtaining consent from patients
- Collection of Patient details
- Collection of Lab and other investigation reports

JULY – AUGUST 2016

- Compilation
- Statistical Analysis
- Submission of Report

10. METHODOLOGY

SITE OF STUDY

The study was carried out in Trichy Diabetes Speciality Centre (P) Ltd., located in Tiruchirappalli, from November 2015 to July 2016. The hospital is unique and well known for its services to people who come from all over the district and various parts of the state.

DEPARTMENTS SELECTED FOR THE STUDY

Patients selected for the study were both in-patients and out-patients

CONSENT FROM HOSPITAL AUTHORITIES

It is customary that every project work carried out in the hospital by the Department of Pharmacy Practice is informed to all physicians, surgeons, and other health care professionals of the hospital after approval. So a protocol of the study, which included the objectives, methodology, etc., was submitted to the chairman of the hospital who is also the Chairperson of the IEC.

The scholar was permitted to utilize the hospital facilities to make a follow up of prescriptions, in the selected departments. All the health care professionals were well informed through official circulars and patients were selected as per selection criteria and their consents were obtained after completely explaining to them about the study.

STUDY DESIGN

DESIGN OF DATA ENTRY FORMAT: (PROFORMA)

A separate data entry format (Proforma) for incorporating patient details was designed.

PROFORMA –I

Patient informed consent form

PROFORMA –II

Patient details such as Name, ID No, Age, Gender , General information like height, weight, BMI, general examination details, provisional diagnosis, diabetic and hypertensive history, social history, family history of diabetes.

PROFORMA –III

Investigation chart – it includes values of diabetic profile study, lipid profile study, and biochemistry.

PROFORMA –IV

Medication chart

PATIENT SELECTION CRITERIA

INCLUSION CRITERIA

- Type -2 Diabetes mellitus
- Insulin unexposed patients
- Both genders
- Age above 18 yrs and below 80 years

EXCLUSION CRITERIA

- Pancreatitis
- Pregnancy
- Breast feeding
- Renal insufficiency
- Hepatic insufficiency
- Malignancy

STUDY GROUP

S.NO	STUDY GROUP	STUDY DRUGS
1.	**Group A** **(n = 55)**	**Metformin & a Sulphonyl urea***
2.	**Group B** **(n = 50)**	**Metformin+ a Sulphonyl urea* +SGLT2-I****

* Sulphonylurea used included either Gliclazide or Glimepiride

**SGLT2-I used included either Canagliflozin or Dapagliflozin or Empagliflozin.

STATISTICAL ANALYSIS

The collected data was analysed by using suitable statistical methods such as *one – way ANOVA , Column statistics et*c., using the statistical software *"Graph pad – prism 5 for windows version 5.01"*

11. RESULTS AND DISSCUSSION

This project is designed to study the efficiency of SGLT2 inhibitors in NIDDM patients on the backdrop use of metformin and a sulphonyl urea. This study included 105 type 2 diabetes patients, based on inclusion and exclusion criteria after letting out the drop outs numbering 19.

From the selected 105 patients, 55 patients were treated with **Metformin and a Sulphonyl Urea (Gliclazide / Glimepiride)** combination that were termed **Group A** and remaining 50 patients were treated with **Metformin + a Sulphonyl urea + a SGLT2- I (Canagliflozin 100mg or Dapagliflozin 10mg or Empagliflozin 10mg)** combination that were termed **Group B.**

In this study the initial readings were considered as base values, after which each month values were taken for FPG (Fasting plasma glucose), PP (Post prandial plasma glucose), Body weight in kg etc., and for HbA1c (Glycosylated Haemoglobin) in the gap of 3 months once , values were taken.

Categorization of Patients in Group A (n=55) according to Gender:

Out of selected 55 patients, 26 patients (47%) were males, and the remaining 29 patients (53 %) were females. **(Table 10 & Figure 5)**

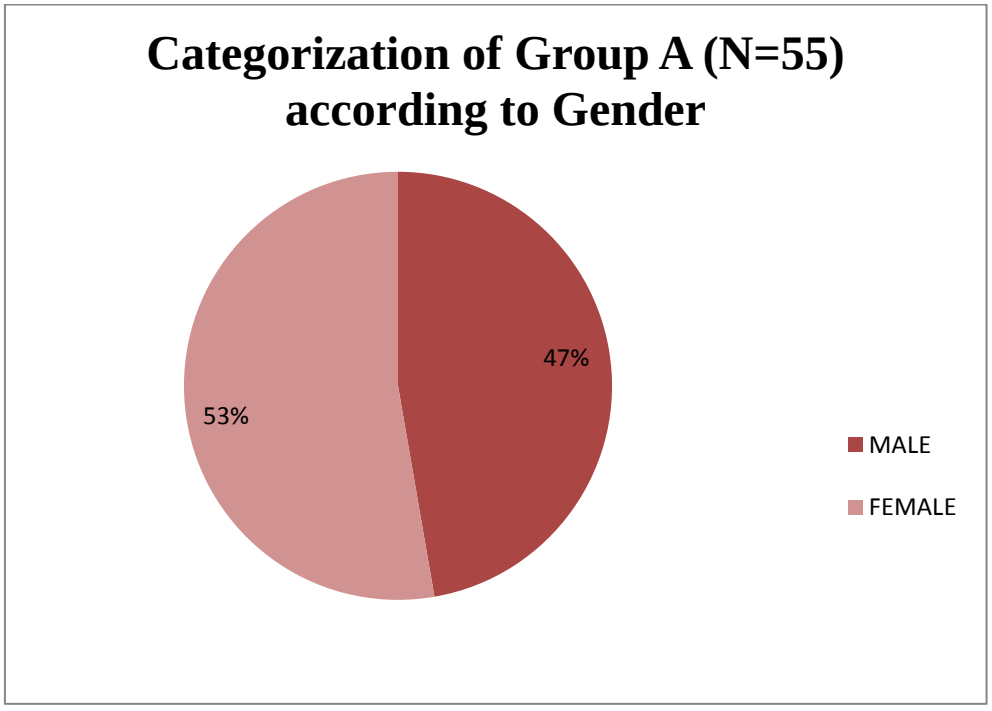
Table 10

Gender wise Categorization of Group A (Met+Su)

n=55

Gender	No. of patients	Percentage (%)
Male	26	47
Female	29	53

Fig. 5



Categorization of Patients in Group B (n=50) according to Gender:

Out of the selected 50 patients , 23patients (46%) were males, and the remaining 27 patients (54 %) were females. **(Table 11 & Figure 6)**

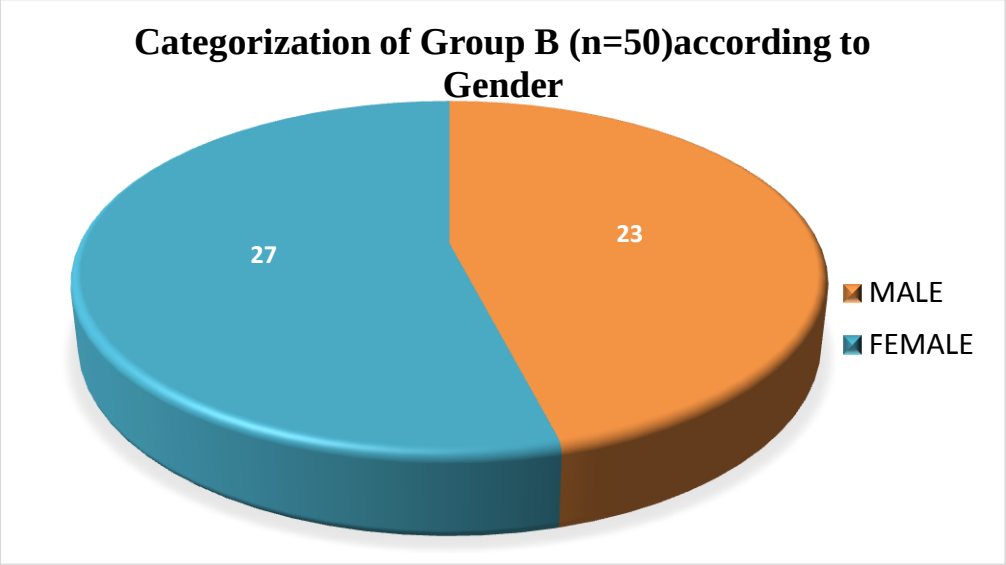
Table 11

Gender wise Categorization of Group B (Met+Su+SGLT2-I)

n=50

Gender	No. of patients	Percentage (%)
Male	23	46
Female	27	54

Fig. 6



The demographic data point towards least variation in the gender wise distribution of the patients included in the study between both the groups.

Categorization of Patients in Group A (n=55) according to Age :

Out of the selected 55 patients, 2 patients (4%) were in the age group of 21-30 years, 9 patients (16%) were in the age group of 31-40 years, 14 patients (25%) were in the age group of 41-50 years, 13 patients (24%) were in the age group of 51-60 years, 11 patients (20%) were in the age group of 61-70 years, 6 patients (11%) were in the age group of 71-80 years . **(Table 12 & Figure 7)**

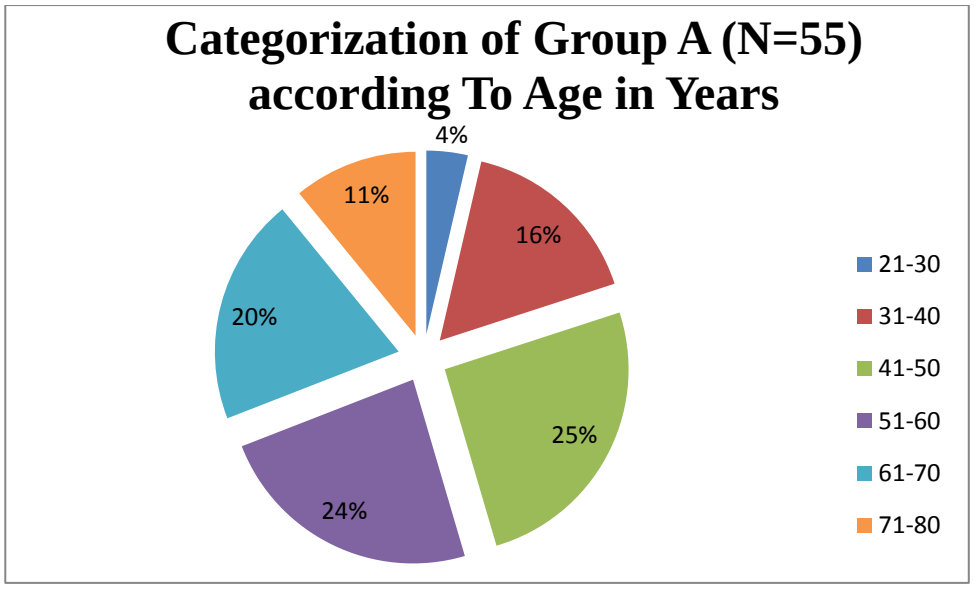
Table 12

Age wise Categorization of Group A (Met+Su)

n=55

Age in years	No. of patients	Percentage (%)
21-30	2	4
31-40	9	16
41-50	14	25
51-60	13	24
61-70	11	20
71-80	6	11

Fig. 7



Categorization of Patients in Group B (n=50) according to Age:

Out of the selected 50 patients, 1 patient (2%) was in the age group of 21-30 years, 10 patients (20%) were in the age group of 31-40 years, 15 patients (30%) were in the age group of 41-50 years, 12 patients (24%) were in the age group of 51-60 years, 9 patients (18%) were in the age group of 61-70 years, 3 patients (6%) were in the age group of 71-80 years. **(Table 13 & Figure 8)**

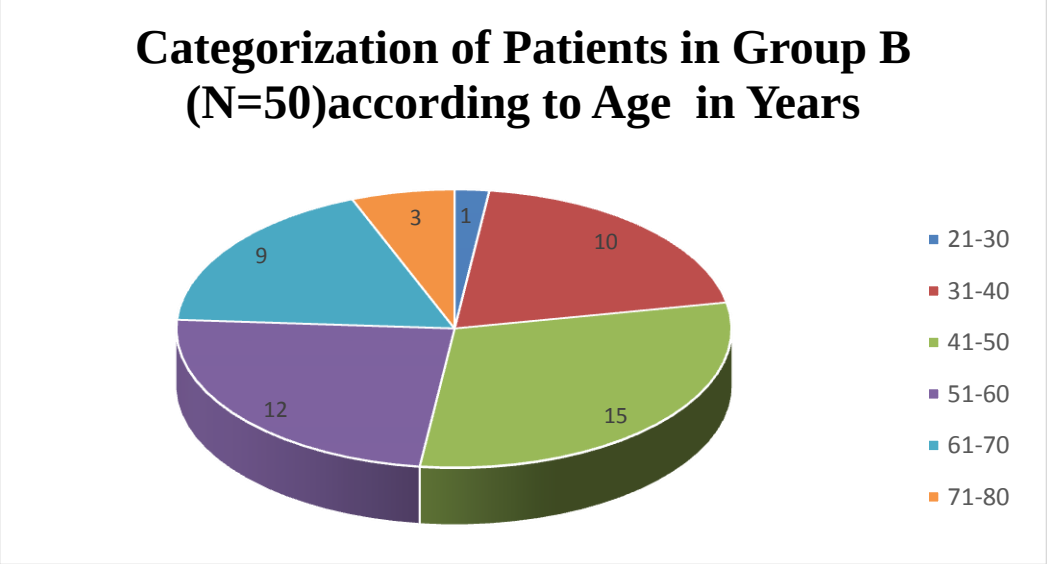
Table 13

Age wise Categorization of Group B (Met+Su+SGLT2-I)

n=50

Age in years	No. of patients	Percentage (%)
21-30	1	2
31-40	10	20
41-50	15	30
51-60	12	24
61-70	9	18
71-80	3	6

Fig.8



Categorization of patients in Group A (n=55) according to their Social Habits:

Out of the selected 55 patients,36 patient (65%) had none of the following habits, 8 patients (15%) were tobacco smokers, 5 patients (9%) were tobacco chewers, 4 patients (7%) were A1coholics, 2 patients (4%) were both A1coholic and tobacco smokers.**(Table 14 &Figure 9)**

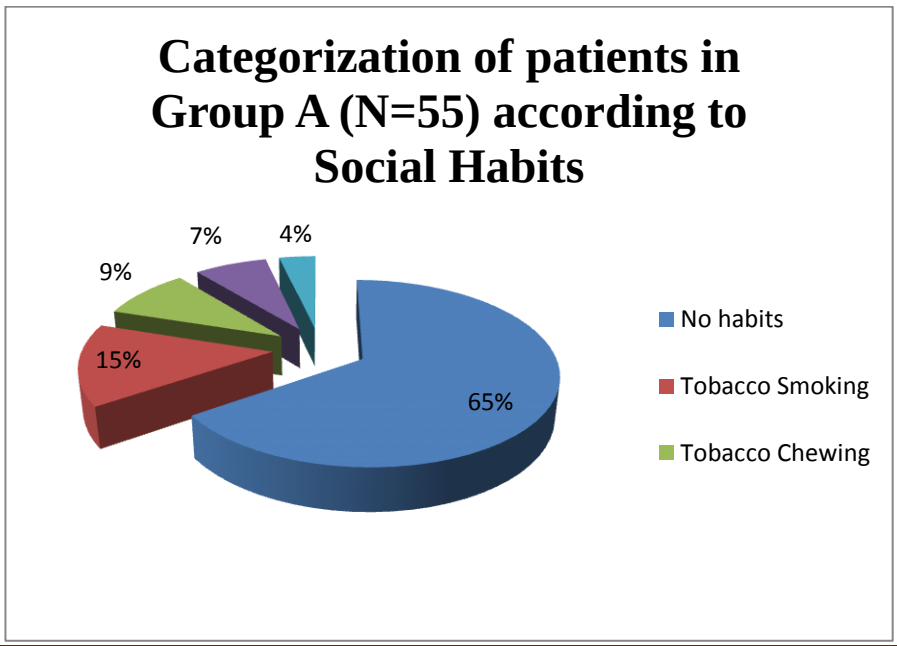
Table 14

Categorization of Group A (Met+Su) according to Social Habits

n=55

Social Habits	No. of Patients	Percentage (%)
No habits	36	65
Tobacco smoking	8	15
Tobacco chewing	5	9
A1cohol Intake	4	7
A1cohol & Tobacco smoking	2	4

Fig. 9



Categorization of Patients in Group B (n=50) according to their Social Habits:

Out of the selected 50 patients, 35 patient (70%) had none of the following habits, 4 patients (8%) were tobacco smokers, 3 patients (6%) were tobacco chewers ,7 patients (14%) were A1coholics,1 patient (2%) was both A1coholic and tobacco smoking.**(Table 15 & Figure 10)**

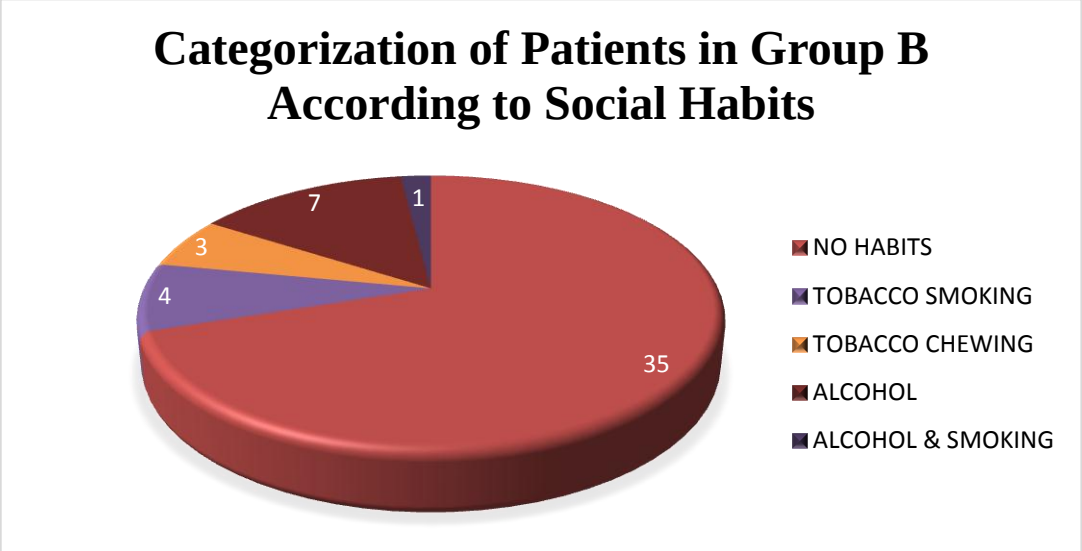
Table 15

Categorization of Group B (Met+Su+SGLT2-I) according to Social Habits

n=50

Social Habits	No. of Patients	Percentage (%)
No habits	35	70
Tobacco smoking	4	8
Tobacco chewing	3	6
A1cohol Intake	7	14
A1cohol & Tobacco smoking	1	2

Fig. 10



The observed data indicates that 65 – 70% of T2DM patients have no particular social habits.

Categorization of patients in Group A (n=55) according to Familial history of DM:

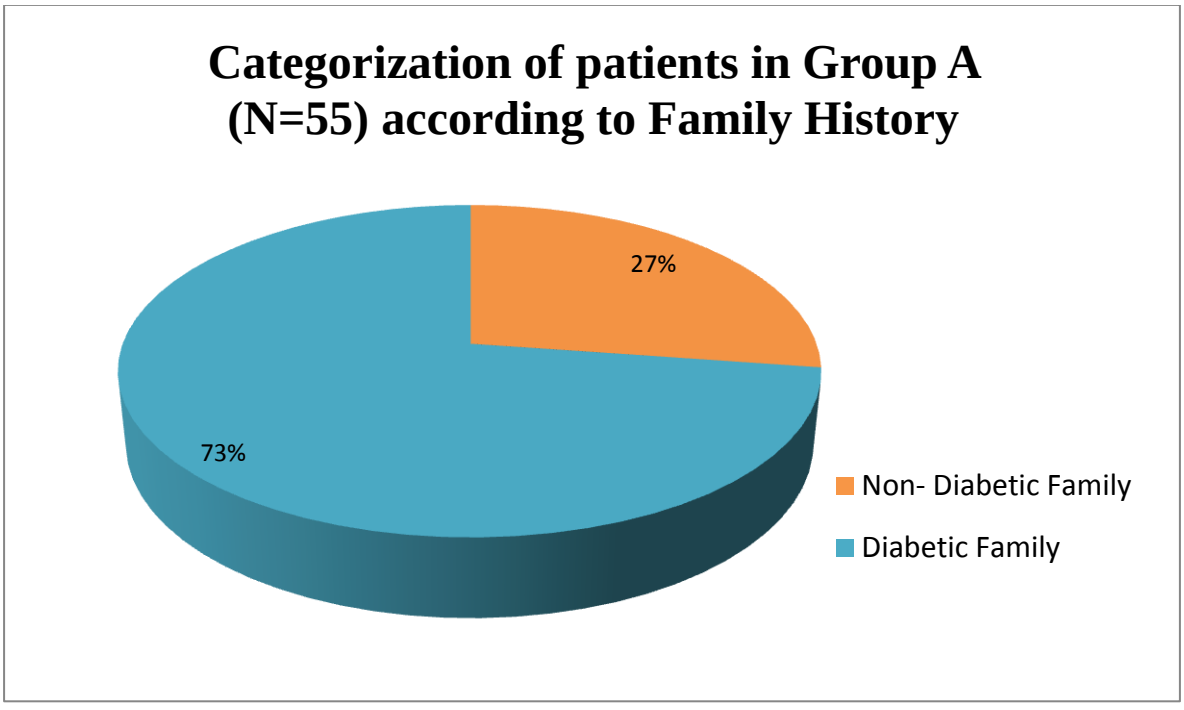
Out of the 55 selected patients, 15 patients (27%) had no familial history of diabetes, 40 patients (73%) had familial history of diabetes of either type 1 or 2**. (Table16 & Figure11)**

Table 16

Categorization of Group A (Met+Su) according to Familial History n=55

Familial history	No. of patients	Percentage (%)
Non-diabetic family	15	27
Diabetic	40	73

Fig. 11



Categorization of patients in Group B (n=50) according to Familial history of DM:

Out of the 50 selected patients, 14 patients (28%) had no familial history of diabetes, 36 patients (72%) had familial history of diabetes. **(Table 17 & Figure 12)**

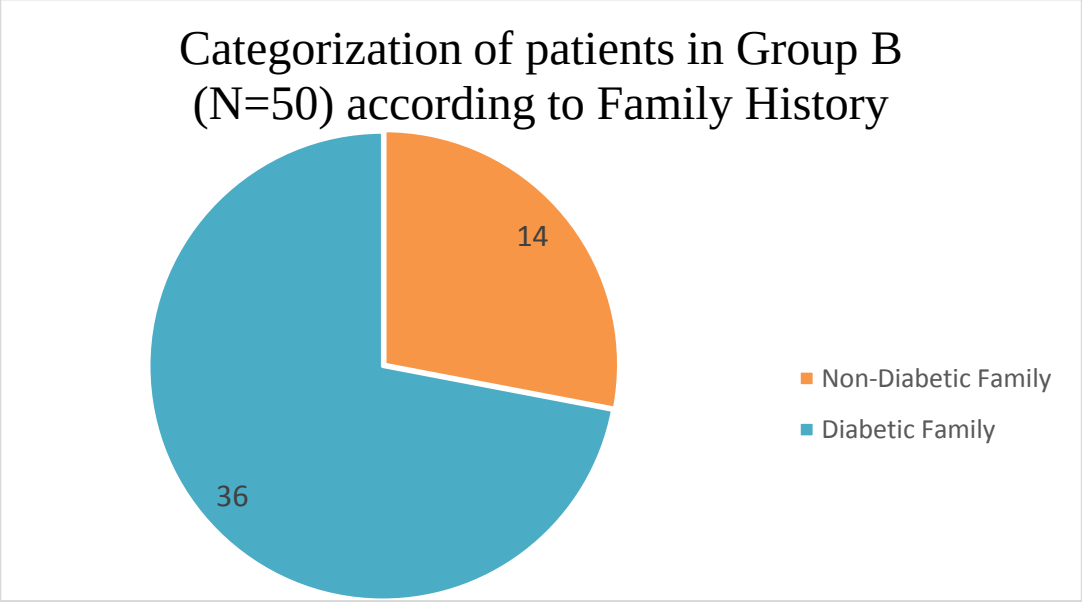
Table 17

Categorization of Group B (Met+Su+SGLT2-I) according to Familial history

n=50

Family history	No. of patients	Percentage (%)
Non-diabetic family	14	28
Diabetic	36	72

Fig. 12



From the above table and figure it is evident that T2DM patients with family history of diabetes is comparatively more than patients with non-diabetic family history.

Categorization of patients in Group A (n=55) according to their Food Habits:

Out of the 55 selected patients, 31 patients (56%) are vegetarians, 24 patients (44%) are having mixed diet. **(Table 18 & Figure 13)**

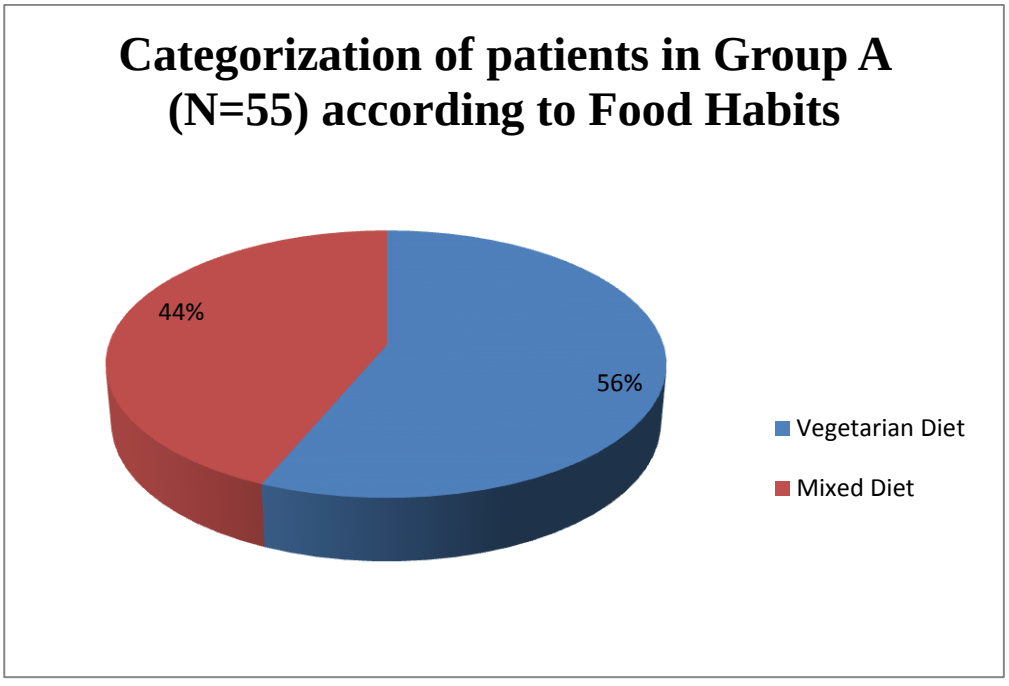
Table 18

Categorization of Group A (Met+Su) according to Food Habits

n=55

Food Habit	No. of patients	Percentage (%)
Vegetarian diet	31	56
Mixed diet	24	44

Fig. 13



Categorization of patients in Group B (n=50) according to their Food Habits:

Out of the 50 selected patients, 18 patients (36%) are vegetarian, 32 patients (64%) are having mixed diet. **(Table 19 & Figure 14)**

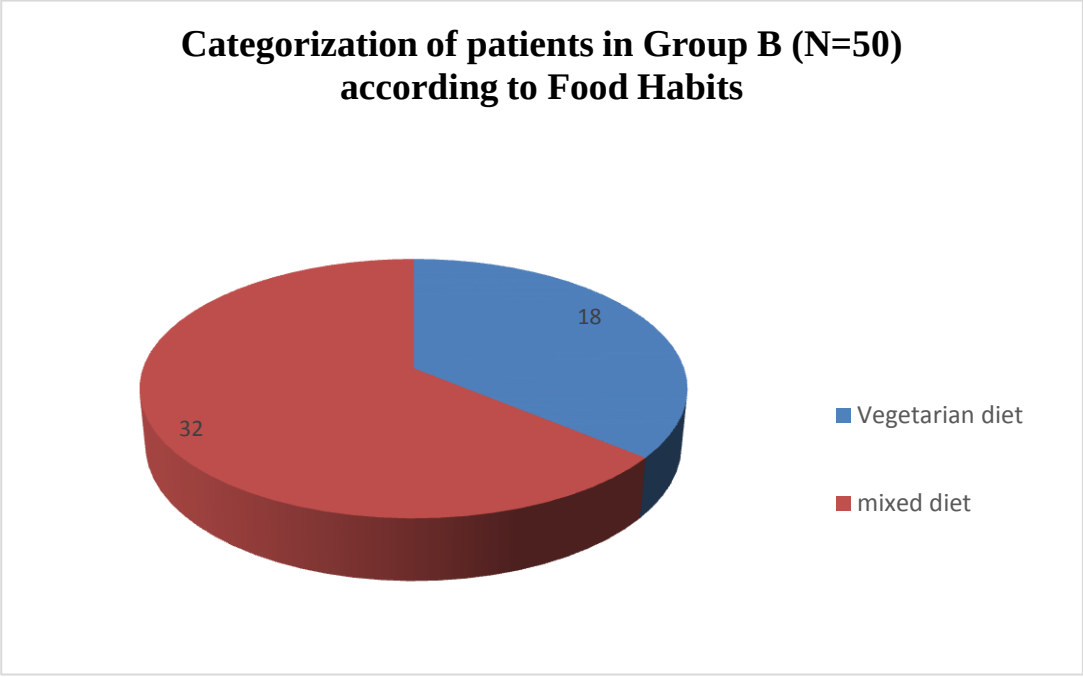
Table 19

Categorization of Group B (Met+Su+SGLT2-I) according to Food Habits

n=50

Food Habits	No. of patients	Percentage(%)
Vegetarian diet	18	36
Mixed diet	32	64

Fig. 14



Categorization of patients in Group A (n=55) according to BMI:

Out of the 55 selected patients, 12 patients (22%) were of normal weight, 26 patients (47%) were overweight, 8 patients (15%) were in the obese class I criteria, 6 patients (11%) were in the obese class II criteria, 3 patients (5%) were in obese class III criteria. **(Table 20 & Figure 15)**

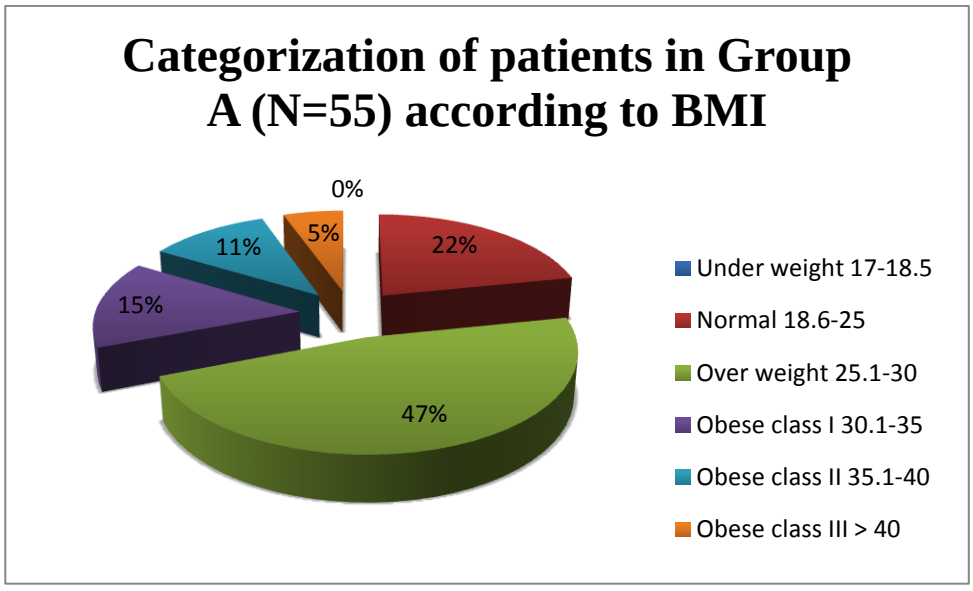
Table 20

Categorization of Group A (Met+Su) according to BMI

n=55

Body mass index kg/m^2	No. of patients	Percentage (%)
Under weight 17 - 18.5	0	0
Normal 18.6 - 25	12	22
Overweight 25.1 - 30	26	47
Obese class I 30.1 - 35	8	15
Obese class II 35.1 - 40	6	11
Obese class III > 40	3	5

Fig. 15



Categorization of patients in Group B (n=50) according to BMI:

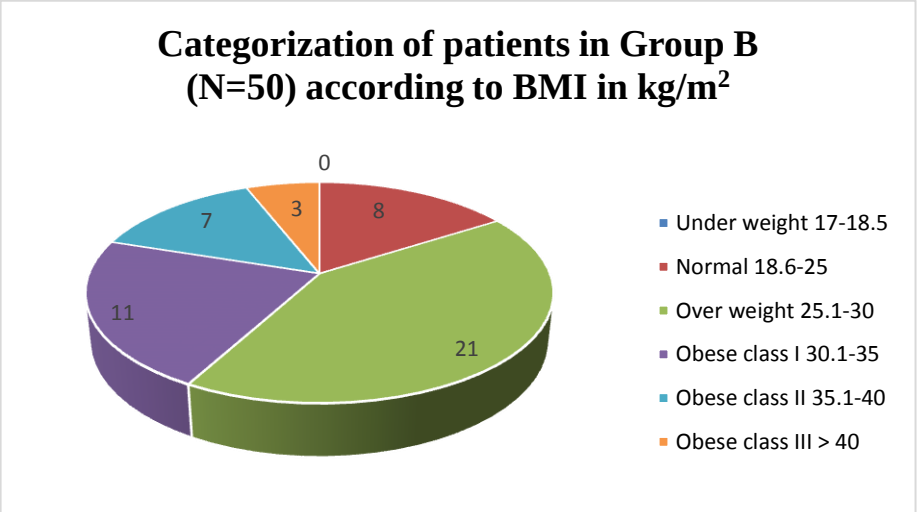
Out of the 50 selected patients, 8 patients (16%) were of normal weight, 21 patients (42%) were overweight, 11 patients (22%) were in the obese class I criteria, 7 patients (14%) were in the obese class II criteria, 3 patients (6%) were in obese class III criteria. **(Table 21 & Figure 16)**

Table 21

Categorization of Group B (Met+Su+SGLT2-I) according to BMI n=50

Body mass index kg/m^2	No. of patients	Percentage (%)
Under weight 17 - 18.5	0	0
Normal 18.6 - 25	8	16
Overweight 25.1 - 30	21	42
Obese class I 30.1 - 35	11	22
Obese class II 35.1 - 40	7	14
Obese class III > 40	3	6

Fig. 16



From the above observed data it is very clear that Overweight, Obese Class I tops the T2DM in both the groups followed by some normal weight, Obese class II & III patients. No under-weight patient is seen with T2DM.

Categorisation of patients in Group A (n=55) according to Associated diseases:

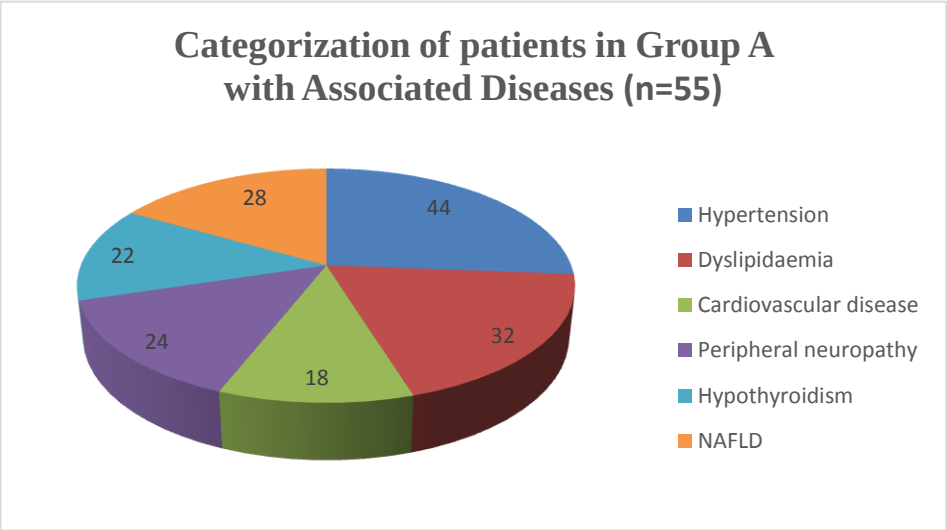
Out of the 55 selected patients,44 patients (26%) has hypertention, 32 patients (19%) has dyslipidaemia, 18 patients (11%) has cardiovascular disease, 24 patients (14%) has peripheral neuropathy, 22 patients (13%) has hypothyroidism, 28 patients (17%) has Non A1coholic Fatty Liver Disease (NAFLD). **(Table 22 & Figure 17)**

Table 22

Categorization of Group A (Met+Su) with Associated Diseases n=55

Associated Disease	No. of patients	Percentage (%)
Hypertension	44	26
Dyslipidaemia	32	19
Cardiovascular disease	18	11
Peripheral neuropathy	24	14
Hypothyroidism	22	13
NAFLD	28	17

Fig. 17



Categorisation of patients in Group B (n=50) according to Associated diseases:

Out of the 50 patients,41 patients (22%) has hypertention,38 patients (21%) has dyslipidaemia, 23 patients (13%) has cardiovascular disease, 33 patients (18%) has peripheral neuropathy, 19 patients(10%) has hypothyroidism, 29 patients (16%) has Non A1coholic Fatty Liver Disease.**(Table 23 & Figure 18)**

Table 23

Categorization of Group B (Met+Su+SGLT2-I) with Associated Diseases

n=50

Associated Disease	No of patients	Percentage (%)
Hypertension	41	22
Dyslipidaemia	38	21
Cardiovascular disease	23	13
Peripheral neuropathy	33	18
Hypothyroidism	19	10
NAFLD	29	16

m

Fig. 18

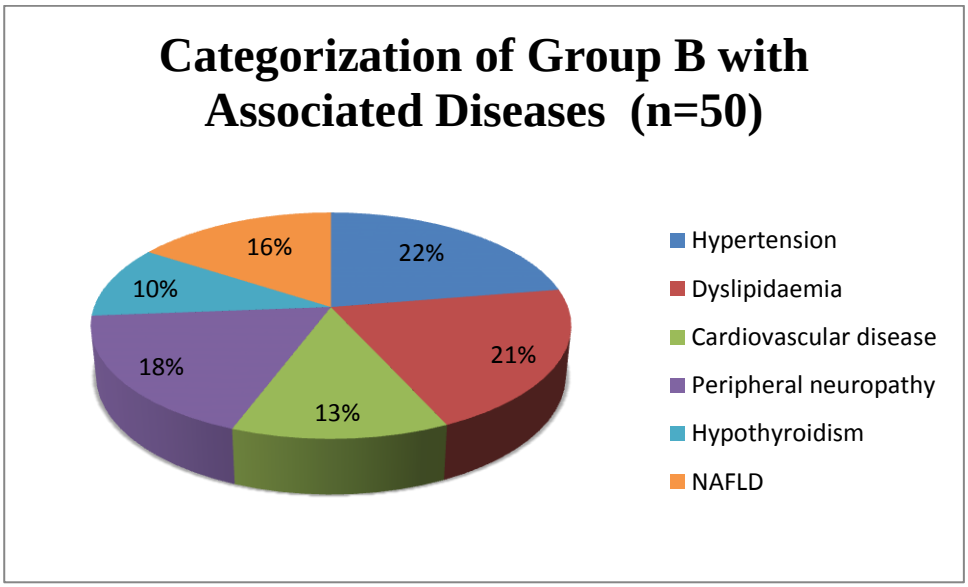


Table 24 shows the values of Fasting blood sugar for Group A (Metformin & a Sulphonyl urea) patients, after every month on taking metformin & a sulphonyl urea keeping the first value as base value.

Table 24

Effect of Group A on Fasting Blood Sugar

(n=55)

PATIENT ID	BASE	REVIEW 1	REVIEW 2	REVIEW 3
A1	125	115	121	108
A2	113	105	111	100
A3	130	126	106	102
A4	94	109	99	105
A5	113	86	83	108
A6	65	88	72	81
A7	123	130	152	131
A8	154	145	142	142
A9	93	78	95	83
A10	145	132	138	114
A11	90	93	94	88
A12	101	102	99	96
A13	91	83	103	82
A14	99	79	79	122
A15	115	104	83	74
A16	135	158	152	146
A17	119	98	105	100
A18	128	118	124	105
A19	134	136	117	108

A20	118	96	124	113
A21	93	97	94	100
A22	157	158	152	150
A23	158	113	109	81
A24	251	214	226	193
A25	109	86	93	88
A26	112	119	119	140
A27	106	87	121	110
A28	113	108	92	96
A29	85	98	88	175
A30	128	94	113	98
A31	98	94	93	90
A32	140	89	88	91
A33	110	119	108	102
A34	134	115	119	112
A35	105	130	122	133
A36	121	108	132	118
A37	81	154	113	126
A38	119	96	123	132
A39	95	96	110	172
A40	82	85	88	84
A41	144	121	121	110
A42	165	127	104	119
A43	113	102	94	84
A44	128	112	119	94

A45	104	142	145	136
A46	99	110	101	97
A47	157	128	116	121
A48	143	126	113	138
A49	149	90	72	66
A50	82	142	142	166
A51	106	145	132	118
A52	132	101	109	105
A53	116	78	95	111
A54	90	94	111	102
A55	145	131	155	113
MEAN ± SE	119.181±3.914	112.545±3.41	113.290±3.447	112.345±3.51
P-Value Vs Base Value by One Way ANOVA		***	***	***

P Value <0.001 *** = Statistically Significant

In the whole group Mean ±SE of the Fasting blood sugar has decreased gradually from 119.181±3.914 to 112.345±3.51 during the therapy.

Table 25 below shows the values of Fasting blood sugar, for Group B (Metformin+ a Sulphonyl urea+SGLT2-I) patients, after every month of taking metformin + a sulphonyl urea +SGLT2-I keeping the first value as the base value

Table 25

Effect of Group B on Fasting Blood Sugar

(n=50)

PATIENT ID	BASE	REVIEW 1	REVIEW 2	REVIEW 3
B1	162	108	113	98
B2	160	111	116	107
B3	211	119	98	96
B4	169	100	98	94
B5	195	180	142	108
B6	106	111	105	98
B7	138	128	115	124
B8	273	222	155	173
B9	261	192	155	126
B10	191	165	136	122
B11	285	214	173	158
B12	104	123	101	98
B13	184	153	127	111
B14	201	121	130	103
B15	200	137	113	118
B16	85	145	122	92

B17	163	123	110	109
B18	185	141	133	110
B19	156	133	102	90
B20	157	118	121	105
B21	180	156	114	98
B22	162	144	118	92
B23	110	114	126	98
B24	201	165	148	102
B25	162	109	77	101
B26	130	107	91	83
B27	145	112	156	125
B28	98	101	116	107
B29	106	101	110	104
B30	85	98	96	101
B31	134	106	119	102
B32	162	153	128	126
B33	174	126	125	108
B34	124	132	128	116
B35	133	146	101	96
B36	195	176	144	128
B37	182	153	112	111

B38	104	163	101	88
B39	158	126	103	98
B40	118	102	109	100
B41	273	186	122	109
B42	101	80	67	110
B43	165	113	122	109
B44	202	173	133	112
B45	195	180	117	102
B46	188	153	112	94
B47	252	145	129	145
B48	166	128	133	111
B49	148	116	121	102
B50	165	123	145	109
MEAN ±SE	166.08±6.771	136.62±4.378	119.76±2.816	108.54±2.331
P-Value Vs Base Value by One Way ANOVA		***	***	***

P Value <0.001 *** = Statistically Significant

In the whole group Mean ±SE of the Fasting blood sugar has decreased significantly from166.08±6.771 to 108.54±2.331 during the therapy

Table 26 shows the values of Post Prandial blood sugar, for Group A (Metformin & a Sulphonyl urea) patients, after every month of taking metformin & a sulphonyl urea keeping the first value as the base value.

Table 26

Effect of Group A on Post Prandial Blood Sugar

(n=55)

PATIENT ID	BASE	REVIEW I	REVIEW II	REVIEW III
A1	91	105	104	96
A2	145	182	128	163
A3	126	146	145	135
A4	106	97	82	97
A5	127	150	156	191
A6	206	191	176	165
A7	150	141	236	124
A8	285	193	182	188
A9	163	130	134	135
A10	210	191	195	197
A11	114	105	130	110
A12	180	164	226	172
A13	146	128	112	118
A14	161	178	154	202
A15	98	138	121	96
A16	143	187	160	161
A17	170	146	168	167
A18	200	183	224	159

A19	91	148	124	159
A20	336	164	155	273
A21	138	149	83	111
A22	187	184	191	154
A23	237	162	160	154
A24	276	265	233	178
A25	136	166	248	169
A26	154	234	224	157
A27	192	158	146	140
A28	141	114	110	108
A29	123	120	158	132
A30	117	127	136	124
A31	130	144	138	94
A32	123	213	152	176
A33	193	186	131	136
A34	178	177	202	199
A35	173	128	165	170
A36	120	192	169	140
A37	203	180	178	175
A38	151	120	166	129
A39	242	139	170	256
A40	126	180	124	133
A41	147	171	163	145
A42	146	250	115	159
A43	146	245	138	140

A44	260	243	210	200
A45	273	206	232	221
A46	226	176	196	199
A47	148	197	152	144
A48	178	136	188	201
A49	232	166	130	129
A50	170	151	164	180
A51	118	241	156	142
A52	283	130	213	210
A53	192	125	134	173
A54	115	179	182	153
A55	124	220	166	172
MEAN ± SE	169.927±7.387	168.018±5.312	162.454±5.231	158.381±5.047
P-Value Vs Base Value by One Way ANOVA		***	***	***

P Value <0.001 *** = Statistically Significant

In the whole group Mean ±SE of the post prandial blood sugar has decreased gradually from 169.927±7.387 to 158.381±5.047during the therapy

Table 27 below shows the values of Post Prandial blood sugar, for Group B (Metformin+ a Sulphonyl urea+ SGLT2-I) patients, after every month of taking metformin + a sulphonyl urea + SGLT2-I keeping the first value as the base value.

Table 27

Effect of Group B on Post-Prandial Blood Sugar

(n=50)

PATIENT ID	BASE	REVIEW I	REVIEW II	REVIEW III
B1	249	140	128	130
B2	243	163	152	145
B3	297	180	106	163
B4	281	218	156	144
B5	207	162	195	188
B6	156	140	131	136
B7	276	203	212	208
B8	348	296	164	180
B9	334	256	190	175
B10	292	186	175	153
B11	352	296	225	246
B12	254	203	167	154
B13	275	226	158	163
B14	291	176	185	154
B15	218	168	154	171
B16	213	195	175	152

B17	214	183	156	142
B18	265	210	172	152
B19	192	176	153	136
B20	139	146	142	148
B21	202	212	145	158
B22	210	183	166	142
B23	207	196	172	155
B24	291	235	182	152
B25	244	166	87	157
B26	207	225	162	145
B27	218	185	197	152
B28	199	163	106	132
B29	141	158	147	132
B30	213	186	165	162
B31	226	176	180	159
B32	245	198	176	198
B33	196	291	195	164
B34	173	100	98	110
B35	235	210	165	154
B36	216	228	173	162
B37	274	186	154	145

B38	256	201	165	173
B39	254	247	167	148
B40	246	202	164	149
B41	325	210	186	185
B42	193	156	138	176
B43	253	186	199	167
B44	253	202	176	132
B45	293	244	165	148
B46	256	198	222	174
B47	314	186	186	193
B48	323	214	176	172
B49	205	183	172	154
B50	199	176	169	165
MEAN ±SE	243.26±7.086	196.52±5.392	165.02±3.953	159.1±3.146
P-Value Vs Base Value by One Way ANOVA		***	***	***

P Value <0.001 *** = Statistically Significant

In the whole group Mean ± SE of the post prandial blood sugar has decreased significantly from 243.26±7.086 to 159.1±3.146 during the therapy.

Table 28 shows the values of Glycosylated Haemoglobin (HbA1c), for Group A (Metformin & a Sulphonyl urea) patients, after every three months of taking metformin & a sulphonyl urea keeping the first value as the base value.

Table 28

Effect of Group A on HbA1c

(n=55)

PATIENT ID	BASE	REVIEW I	REVIEW II
A1	6.5	6.7	6.5
A2	6.3	6.5	6.5
A3	6.8	7	6.8
A4	6.4	5.8	5.6
A5	6.1	6.5	6.3
A6	6	6.5	6.2
A7	6.8	7	6.5
A8	6.8	6.5	6.5
A9	7	6.5	6.3
A10	7.5	6.8	6.2
A11	6.8	6.7	6.5
A12	7.5	7.2	7
A13	6.5	6.3	6.2
A14	7.4	7.1	7.3
A15	6.3	6.3	6.8
A16	8	8.4	8
A17	6.4	6.4	6.6
A18	7.1	7.1	7
A19	7.3	7.3	6.8

A20	7.2	6.5	6.4
A21	6.5	6.2	5.9
A22	7.9	7.6	7.6
A23	8.5	8.2	7.5
A24	8.9	8.5	7.4
A25	6	6.5	6.5
A26	6.5	6.5	6.8
A27	6.9	6.7	6.7
A28	6.6	6	6.2
A29	6.8	7.1	7.8
A30	6.5	6.3	5.8
A31	6.6	6.2	6.2
A32	6.4	6.2	6.6
A33	7.1	7	6.8
A34	7.3	7.5	7
A35	6.8	7	7
A36	6.5	6.9	7.3
A37	8.2	7.7	7.5
A38	7.5	8.3	7.3
A39	8.6	8.4	7.9
A40	6.3	6	6.2
A41	6.8	6.5	6.3
A42	6	6.2	6.4
A43	7.4	7.8	7.2
A44	6.4	6.7	6.2

A45	7	7.2	6.9
A46	6.8	6.5	6.6
A47	6.9	6.7	6.4
A48	6.4	7.4	7.2
A49	7.5	7.4	6.7
A50	7.4	7.1	7.6
A51	7.2	7.2	7.5
A52	7.8	7.6	7.2
A53	6.3	6.5	6.4
A54	6.1	6.6	6.6
A55	7.2	7.3	7.2
MEAN ± SE	6.95±0.090	6.92±0.087	6.77±0.073
P-Value Vs Base Value by One Way ANOVA		***	***

P Value <0.001 *** = Statistically Significant

In the whole group Mean±SE of the Glycosylated Haemoglobin (HbA1c) has decreased gradually from 6.95±0.090 to 6.77±0.073 during the therapy.

Table 29 below shows the values of Glycosylated Haemoglobin (HbA1c), for Group B (Metformin+ a Sulphonyl urea+SGLT2-I) patients, after every three months of taking metformin + a sulphonyl urea +SGLT2-I keeping the first value as the base value

Table 29

Effect of Group B on HbA1c

(n=50)

PATIENT ID	BASE	REVIEW I	REVIEW II
B1	7.8	7.1	6.7
B2	7.1	6.7	6.2
B3	8.2	6.8	6.7
B4	9.1	7.8	7.4
B5	8.3	7.9	6.5
B6	6.7	6.3	5.7
B7	8.4	7.6	6.2
B8	9.6	8.2	7.5
B9	9.7	8.5	7
B10	8.2	7.3	6.8
B11	9.4	8.1	6.9
B12	8.8	7.5	7
B13	8.4	7.2	6.9
B14	10.9	9.1	7.6
B15	7.5	6.9	6.5
B16	7.5	6.5	6.3

B17	8.2	7.4	7
B18	8.8	7.9	7.1
B19	7.4	6.8	6.5
B20	7.1	7	6.8
B21	7.2	6.8	6.5
B22	6.8	6.2	6.5
B23	7.7	7.2	6.9
B24	7.5	7	6.5
B25	9	8.2	7.1
B26	8.2	7.3	6.5
B27	7.8	7.6	7.6
B28	6.8	7.1	6.6
B29	7.4	7.1	6.8
B30	6.5	6.8	6.3
B31	7.5	7.2	6.6
B32	7.8	7	7
B33	8.5	7.8	6.5
B34	9.6	6.5	6.4
B35	8.4	7.5	7.5
B36	8.6	7.9	6.4
B37	7.5	7	6.8

B38	8.2	7.5	7.1
B39	6.9	6.2	6.4
B40	7.8	6.5	6.2
B41	9.8	7.7	7
B42	7.2	6.5	6.7
B43	7.8	7	7
B44	8.3	7.6	6.4
B45	9.4	7.6	6.8
B46	7.9	7.3	6.2
B47	9.3	8	6.8
B48	7.9	7	6.5
B49	7.4	7	6.5
B50	8.1	7.2	7
MEAN ±SE	8.118±0.131	7.278±0.084	6.728±0.055
P-Value Vs Base Value by One Way ANOVA		***	***

P Value <0.001 *** = Statistically Significant

In the whole group Mean±SE of the Glycosylated Haemoglobin (HbA1c) has decreased significantly from 8.118±0.131 to 6.728±0.055 during the therapy.

Table 30 shows the values of Body weight in Kg, for Group A (Metformin & a Sulphonyl urea) patients, after every month of taking metformin & a sulphonyl urea keeping the first value as the base value.

Table 30

Effect of Group A on Body Weight in Kg

(n=55)

PATIENT ID	BASE	REVIEW I	REVIEW II	REVIEW III
A1	68	67	65.3	66
A2	64	64	63	62
A3	105.55	103	101	98
A4	78	77	77	75
A5	62	61.7	60.2	59.3
A6	72	72	71	69.7
A7	66.85	68.3	69.1	68.8
A8	59.75	59	58.5	56.7
A9	64	63	62	62
A10	68	67	67	65
A11	82	81.3	79.2	78.2
A12	52.4	52	52	51.2
A13	76	75	75	74.2
A14	79	81	80	80
A15	54	56	54	54
A16	66.2	66	67.4	67
A17	49.65	49.65	49	51.3
A18	85.25	86	84	83
A19	66	66	65	66

A20	58	58	58	58
A21	61.6	62.75	61	61
A22	77	76	75	75
A23	58	57.4	56.6	56
A24	78	77.8	77	76
A25	75	75	75	74
A26	55.5	55.8	55	57
A27	48	48	48	48.8
A28	66	64.24	65	65
A29	62	64.45	66	65
A30	53	53	52	52
A31	72	74	74	75
A32	61	62	63.9	64.85
A33	53	53	53	53
A34	72	70	71	71.5
A35	55.9	55	55	55
A36	64	64	65.3	65
A37	74	75.3	77	76.4
A38	56	58	57	56
A39	64	64	64	65
A40	74	74	73	72
A41	63.3	64	64	63
A42	49	48	49	50
A43	53.75	53.1	53	53
A44	78	77.4	77	76

A45	103.5	101	100	99.5
A46	63	62.4	62	60.5
A47	66	66	61	61
A48	78	77	74	73
A49	58	57.8	57	56.4
A50	65	65	65	64
A51	53.5	53.8	55	55.4
A52	55	54	54	52
A53	61	61	62	60
A54	61	61	60	58.5
A55	69.9	68.85	67.6	66
MEAN ± SE	66.083±1.583	65.946±1.583	65.492±1.542	65.040±1.458
P-Value Vs Base Value by One Way ANOVA		***	***	***

P Value <0.001 *** = Statistically Significant

In the whole group Mean±SE of the Body weight has decreased gradually from 66.083±1.583to 65.040±1.458 during the therapy.

Table 31 shows the values of Body weight in Kg, for Group B (Metformin+aSulphonyl urea+SGLT2-I) patients, after every month of taking metformin + a sulphonyl urea +SGLT2I keeping the first value as the base value.

Table 31

Effect of Group B on Body Weight in Kg

(n=50)

PATIENT ID	BASE	REVIEW I	REVIEW II	REVIEW III
B1	58	56	55	54
B2	63.55	63.25	62	62
B3	63	63	63	52
B4	57.5	56	57	57
B5	53.15	51.55	50	49
B6	63	63	62	61
B7	84.05	81.05	79	78
B8	117.3	115	113.5	111
B9	84.6	81.7	79.2	78
B10	55.9	55.2	54	53
B11	69.5	67.5	66	65.4
B12	76	77	74.24	72
B13	73	71	68.9	67.5
B14	91.8	90	89	87
B15	59	54.5	54	50.3
B16	74.5	72.3	71	70

B17	87	85	82	81
B18	76	74.5	73.2	71.3
B19	72	69	68.3	66.5
B20	79.2	77.8	76.5	74.9
B21	67.5	66	64.6	63
B22	75	73.3	71.8	70
B23	74.4	73	71.6	68.3
B24	92	91.3	88.5	87.2
B25	58.8	57.6	55	54
B26	74	72	71.9	67
B27	68	66.2	65	63.7
B28	63	62	61.3	60
B29	58.15	56.3	54.7	53
B30	74.5	73.2	71	68.4
B31	83	81.9	80.2	78
B32	77	75.6	76	75
B33	92	90	88.6	87
B34	63	61	58.5	55
B35	98	96	94.4	92
B36	88	87	85.3	85
B37	75	73.2	71.1	70

B38	79	78	76.2	74
B39	65.4	64	63.3	63
B40	73	71	69.4	67.6
B41	77	74	72.6	71
B42	67.5	66.7	65	63.8
B43	76	75.4	74	72.2
B44	91	89.4	88	86.5
B45	75	73.2	73	72.3
B46	72	71.2	70	68.4
B47	78	77.3	75.3	74
B48	82	80.2	77.6	77
B49	69	68.2	66.6	65
B50	74	72.1	71	69.4
MEAN ±SE	74.366±1.716	72.813±1.703	71.386±1.672	69.634±1.689
P-Value Vs Base Value by One Way ANOVA		***	***	***

P Value <0.001 *** = Statistically Significant

In the whole group Mean±SE of the Body weight has decreased significantly from 74.366 ± 1.716 to 69.634 ± 1.689 during the therapy.

Comparative Mean Reduction in FPG of Group A and Group B

Table 32 shows in **Group A** (Metformin + a Sulphonyl urea) patients (n=55), the mean value change of fasting blood sugar at the base line was 119.181 ±3.914 and after treatment for a mean period of 6 months, it was observed 112.345 ±3.51.

In **Group B** (Metformin+aSulphonyl urea+SGLT2-I) patients (n=50) the mean value change of fasting blood sugar at the base line was 166.08 ±6.77and after treatment for a mean period of 6 months, it was observed 108 ± 2.33.

In Group A (Metformin + a Sulphonyl urea) patients (n=55), the percentage mean change value is **5.70%**

In Group B (Metformin+a Sulphonyl urea+SGLT2-I) patients (n=50) the percentage mean change value is **34.67%**

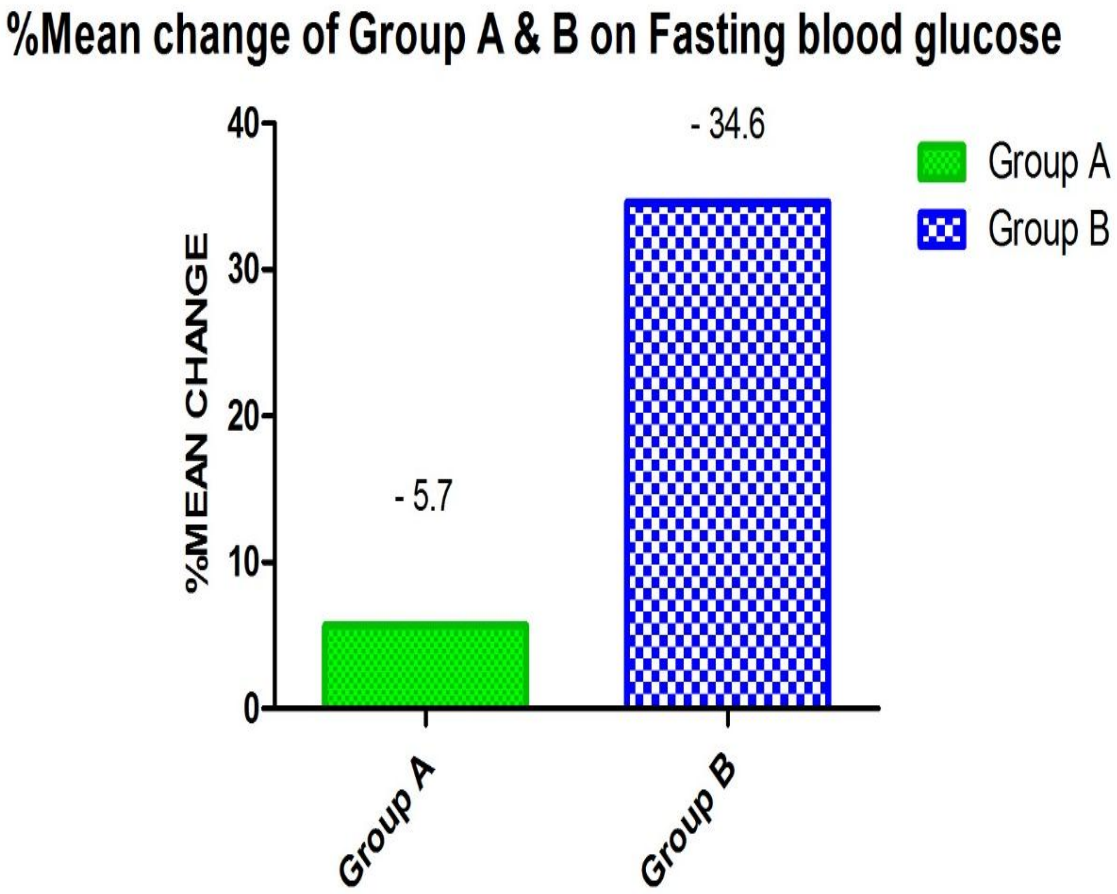
Table 32

Mean ± SE Reduction in FPG of

Group A and Group B

Groups	No. of patients	Mean ± SE Change of Group A & B in FPG mg/dL				% mean Reduction
		Base	Rev I	Rev II	Rev III	
Group A Metformin+sulphonyl urea	55	119.181 ± 3.914	112.545 ± 3.410	113.290 ± 3.447	112.345 ± 3.51	**5.70**
Group B Metformin+sulphonyl urea + SGLT2-I	50	166.08 ± 6.77	136.6 ± 4.378	119.7 ± 2.816	108 ± 2.33	**34.67**

Fig. 19


%Mean change of Group A & B on Fasting blood glucose
%MEAN CHANGE
40
30
20
10
0
- 34.6
- 5.7
Group A
Group B
Group A
Group B

Comparative Mean Reduction in PPPlasma Glucose of Group A & B

Table 33 shows in Group A (Metformin + a Sulphonyl urea) patients (n=55), the mean value change of Post Prandial blood sugar at the base line was169.927 ±7.387 and after treatment for a mean period of 6 months, it was observed 158.381±5.047.

In Group B (Metformin+aSulphonyl urea+SGLT2-I) patients (n=50) the mean value change of Post Prandial blood sugar at the base line was 243.2±7.086 and after treatment for a mean period of 6 months, it was observed 159.1±3.146.

In Group A (Metformin + a Sulphonyl urea) patients (n=55), the percentage mean change value is **6.79%**

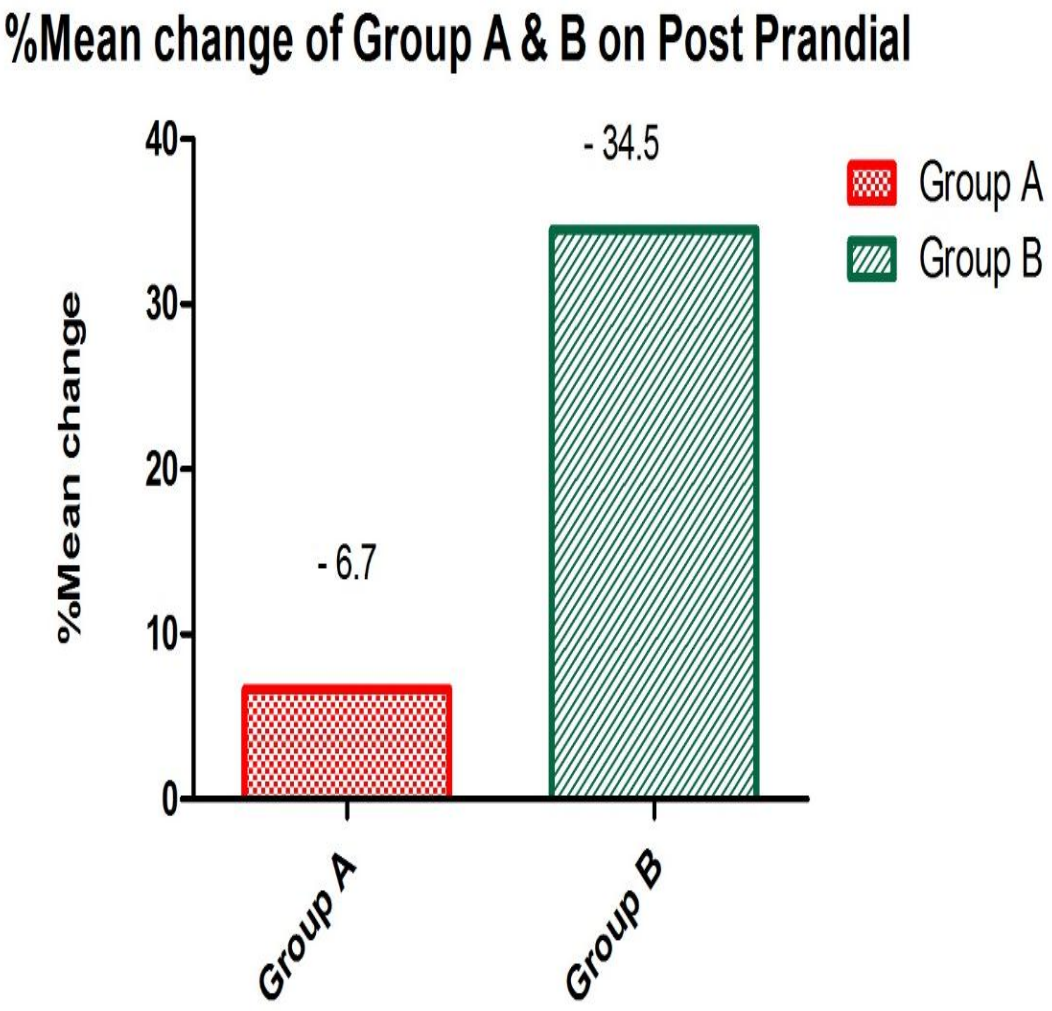
In Group B (Metformin+aSulphonyl urea+SGLT2-I) patients (n=50) the percentage mean change value is **34.58%**

Table 33

Mean ± SE Reduction in PostPrandial (PP) Plasma Glucose of Group A and Group B

Groups	No.of patients	Mean ± SE Change of Group A & B in PP mg/dL				% mean Reduction
		Base	Rev I	Rev II	Rev III	
GroupA Metformin+sulphonyl urea	55	169.927 ± 7.387	168.018 ± 5.312	162.45 ± 5.231	158.381 ± 5.047	**6.79**
GroupB Metformin+sulphonyl urea + SGLT2-I	50	243.2 ± 7.086	196.5 ± 5.392	165.02 ± 3.953	159.1 ± 3.146	**34.58**

Fig. 20


%Mean change of Group A & B on Post Prandial
%Mean change
40
30
20
10
0
- 6.7
- 34.5
Group A
Group B
Group A
Group B

Comparative Mean Reduction in HbA1c of Group A and B

Table 34 shows in Group A (Metformin + a Sulphonyl urea) patients (n=55), the mean value change of Glycosylated Haemoglobin (HbA1c) at the base line was 6.95±0.090 and after treatment for a mean period of last 3 months, it was observed to be 6.77±0.073.

In Group B (Metformin+aSulphonyl urea+SGLT2-I) patients (n=50) the mean value change ofGlycosylated Haemoglobin (HbA1c) at the base line was 8.1±0.131 and after treatment for a mean period of last 3 months, it was observed to be 6.7±0.055.

In Group A (Metformin + a Sulphonyl urea) patients (n=55), the percentage mean change value is **2.5%**

In Group B (Metformin+aSulphonyl urea+SGLT2-I) patients (n=50) the percentage mean change value is **7.28%**

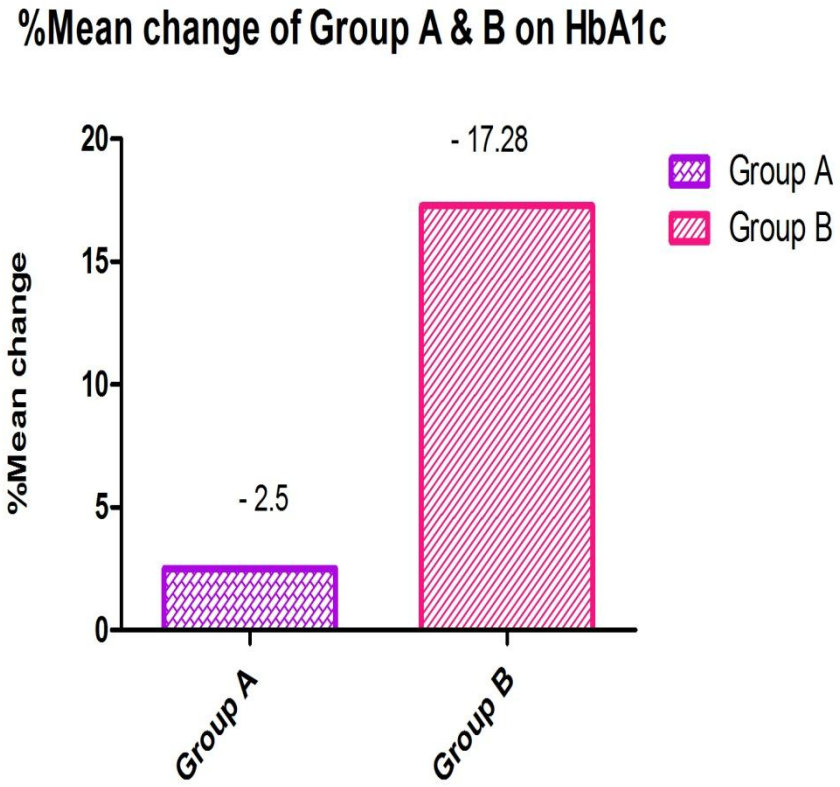
Table 34

Mean ± SE Reduction in HbA1c Value of

Group A and Group B

Groups	**No.of patients**	**Mean ± SE Change of Group A & B in HbA1c in %**			**% mean Reduction**
		Base	**Rev I**	**Rev II**	
GroupA Metformin+sulphonyl urea	55	6.95±0.090	6.92±0.087	6.77±0.073	**2.5**
Group B Metformin+sulphonyl urea + SGLT2-I	50	8.1±0.131	7.2± 0.084	6.7±0.055	**7.28**

Figure 21


%Mean change of Group A & B on HbA1c
%Mean change
20
15
10
5
0
- 17.28
- 2.5
Group A
Group B
Group A
Group B

Comparative Mean Reduction in Body Weight of Group A and B

Table 35 shows in Group A (Metformin + a Sulphonyl urea) patients (n=55), the mean value change of Body weight in Kg at the base line was 66.083±1.583 and after treatment for a mean period of 6 months, it was observed 65.040±1.458.

In Group B (Metformin+a Sulphonyl urea+SGLT2-I) patients (n=50) the mean value change of Body weight in Kg at the base line was 74.366±1.716 and after treatment for a mean period of 6 months, it was observed 69.63±1.689.

In Group A (Metformin + a Sulphonyl urea) patients (n=55), the percentage mean change value is **1.57%**

In Group B (Metformin+aSulphonyl urea+SGLT2-I) patients (n=50) the percentage mean change value is **6.28%**

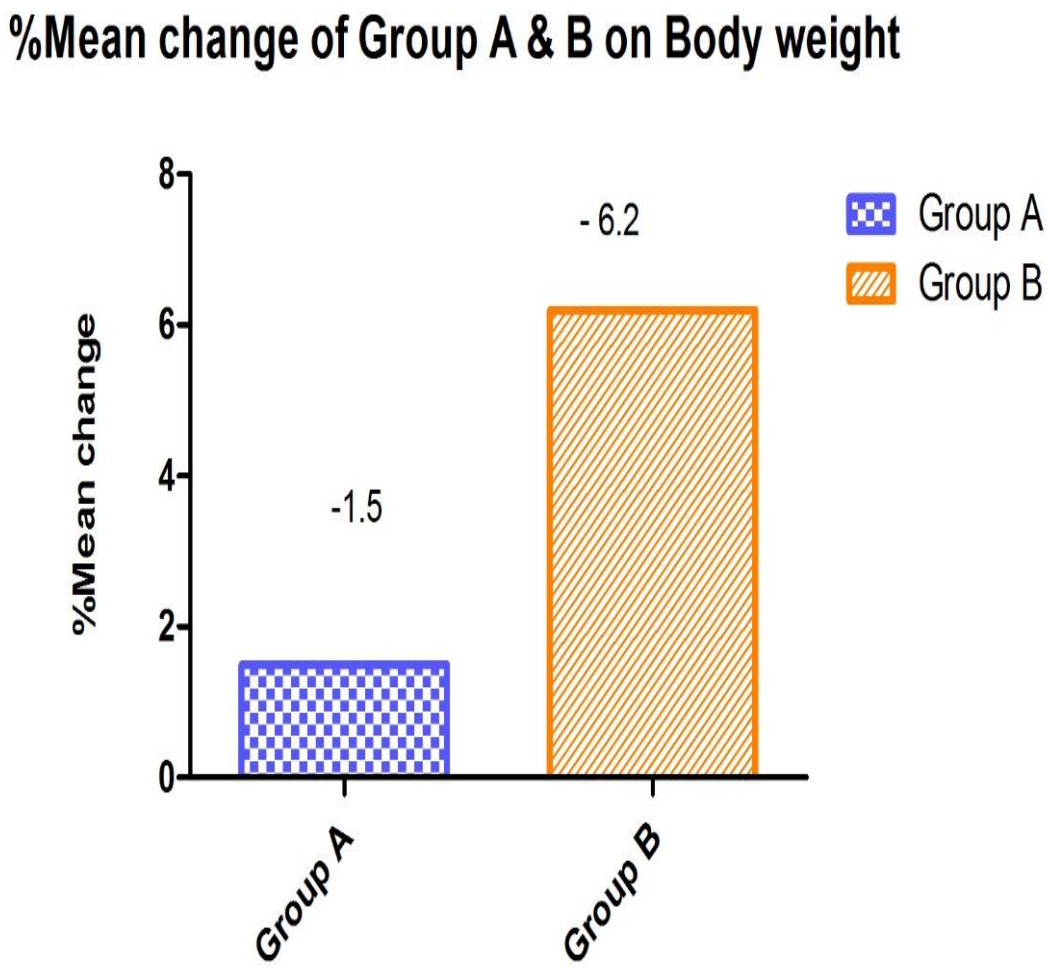
Table 35

Mean ± SE Reduction in Body Weight in Kg of

Group A and Group B

Groups	No.of patients	Mean ± SE Change of Group A & B in Body weight in kg				% mean Reduction
		Base	Rev I	Rev II	Rev III	
Group A Metformin+sulphonyl urea	55	66.083± 1.583	65.946± 1.583	65.492± 1.542	65.040± 1.458	**1.57**
Group B Metformin+sulphonyl urea + SGLT2-I	50	74.366± 1.716	72.8± 1.703	71.3± 1.672	69.63± 1.689	**6.28**

Figure 22


%Mean change of Group A & B on Body weight
%Mean change
8
6
4
2
0
- 6.2
-1.5
Group A
Group B
Group A
Group B

12. CONCLUSION

- This study included 105, T2DM patients of which, patients in the age group of 21 to 30 yrs on one end and 71 to 80 yrs on the other were a bare minimal on both the groups. Further the social habits, food habits being a vegan or non-vegetarian were also equally distributed amongst the two groups. About familial history of Diabetes with the patients, it was 73% in Group A and 72% in Group B. Patients with normal weight were 22% in Group A and 16% in Group B of the Body Mass Index. 5% patients were under Class III category of obesity in Group A whereas it was 6% in Group B. All the above parameters are placed of equal distribution, thereby variables are kept at a bare minimum **not** jeopardizing the observed results in any way

- F. P. G. values showed a reduction of **5.7%** from base value in Group A; whereas the same was showing a significant **34.64%** reduction in Group B patients

- The post prandial glucose measurement showed a **6.79%** reduction in Group A and **34.58%** reduction in Group B patients

- The HbA1c values showed a **2.59%**reduction in Group A and a very significant **7.28%** reduction in Group B cases

- Ultimately the reduction in Body Mass Index was **1.57%**in Group A and **6.28%** in Group B patients

- The outcome of this study clearly shows that addition of a SGLT2 inhibitor drug to the conventional oral regime of type II diabetes with metformin and a sulphonyl urea has a marked and significant advantage over the biguanide + sulphonyl urea only combination considering all the parameters that showa better and significant control of the blood glucose level and the Body Mass Index.

- Hence T2DM may conveniently be treated with metformin and a sulphonyl urea with the addition of a SGLT2 Inhibitor for a significantly improved life of patients.

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17.11.2015

Approval of Ethics Committee

The Institutional Ethics Committee of the Periyar College of Pharmaceutical Sciences, Tiruchirapalli - 21 (concerning clinical work being carried out at Trichy Diabetes Speciality Centre (P) Ltd., Tiruchirapalli-18), reviewed and discussed the application of **Mrs. M. Srividhya** (II-M.Pharm) to conduct Clinical evaluation entitled **"Efficacy and usefulness of SGLT2 Inhibitors in NIDDM Patients on the backdrop of Metformin and Sulphonyl Urea"** on 19.11.2015.

The following documents were reviewed:

a) Study Protocol
b) Patient Information Sheets
c) Investigator's Broucher
d) Methods for patient accrual proposed to be used for the purpose
e) Investigator's Undertaking

The following are the members of the Ethics Committee

Dr. M. Shunmugavelu, M.D.,	.. Chairman
Dr. A. M. Ismail, M Pharm., Ph.D.,	.. Member-Secretary
Dr. R. Senthamarai, M.Pharm., Ph.D.,	.. Consultant Pharmacist
Dr. V. Ravindranath, MBBS., MDC(New Castle)..	.. Consultant Diabetologist
Mr. K. Sakthivel, M. Pharm.,	.. Senior Pharmacist
Ms. Gracey G. George	.. Social Worker
Mr. A. Periasamy, B.Com., B.L.,	.. Advocate of Law

We approve the study to be conducted in its presented form. The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information and asks to be provided a copy of the final report.

Secretary, Institutional Ethics Committee
Periyar College of Pharmaceutical Sciences

PATIENT INFORMED CONSENT FORM

PROFORMA –I

PATIENT NAME : **DATE:**

AGE: **SEX:**

I was explained about the description of the research study and they have answered all the questions I have at this time.

I freely volunteer to participate in this study. I understand that I need not have to take part in this study and that my refusal to participate will involve no penalty. Further I understand that I am free to discontinue participation from this study at any time.

Clinician's name: **Signature of the patient**

mwptpf;fg;gl;l KbT

Nehahspapd; ngah;: **Njjp :**

taJ: **ghypdk; :**

vdf;F Muha;r;rp Ma;T tpsf;fk; gw;wp KOtJkhf tpsf;fpaNjhL> ehd; Nfl;l midj;J re;Njfq;fSf;Fk;, jpUg;jpfukhf gjpy; mspj;jdh;.

ehd; KOkdjhf ,e;j Ma;tpy; gq;Nfw;f rk;kjpf;fpNwd;. ,e;j Ma;tpy; vd; clw;rk;ke;jg;gl;l gq;Nfw;G vJTk; ,y;iy vdTk;> ,jpy; ehd; gq;Nfw;f;f kWg;gjpdhy; vdf;F mguhjk; vJTk; ,y;iy vdTk;> kw;Wk; ,e;j Ma;tpy; ,Ue;J ve;j NeuKk; ehd; tpyfpf;nfhs;s vdf;F chpik cz;L vd;gijAk;, ehd; Ghpe;J nfhz;Nld;.

kUj;Jthpd; ngah; **Nehahspapd; ifnahg;gk;**

PROFORMA – II

PATIENT DETAILS

PATIENT ID:

GENDER: M/F AGE: D.O.B:

MARITAL STATUS:

REVIEW ON

CONSULTANT NAME:

STUDY GROUP: A ☐ B ☐

GENERAL INFORMATION:

HT: WT: BMI: IBW:

HISTORYOF ILLNESS

TIME OF ONSET / YEAR DIAGNOSED:

DURATION:

FAMILY HISTORY OF DIABETES:

Father/Mother/Siblings/Others/Nil

HYPERTENSION: YES / NO DURATION:

PAST MEDICAL HISTORY:

PAST MEDICATION HISTORY:

SOCIAL HISTORY:

HABITS	PREVIOUS	NOW	
		REGULAR	IRREGULAR
Alcohol			
Tobacco Smoking			
Tobacco Chewing			
Veg / Non-Veg			

PHYSICAL ACTIVITY:

COMPLAINTS:

DIAGNOSIS:

PROFORMA III

DIABETIC PROFILE

S.No.	Test	Reference Value mg/dL	Results mg/dL					
			R1	R2	R3	R4	R5	R6
1.	Fasting	70-100						
2.	PP	<140						
3.	GRBS	Below 200						
4.	HbA1c	6-7 % good control 7-8% fair control 8-10 % unsatisfactory control Above 10% poor control						

PROFORMA IV

MEDICATION CHART:

S.No.	Brand Name	Generic Name	Dose	Route	Frequency	Prescribed During Review No.					
						R1	R2	R3	R4	R5	R6
Date											
1.											
2.											
3.											
4.											
5.											
6.											
7.											
8.											
9.											
10.											
11.											
12.											
13.											
14.											
15.											